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Investigation of Selected Potential Environmental Contaminants Benzotriazoles

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16. ABSTRACT

Benzotriazoles are produced in approximately 5-6 million pounds per year in the United States. The majority are used in anticorrosion applications. Approximately 20-30% are used as UV stabilizers, many of which are 2-substituted benzotriazoles. Small amounts are used for photographic applications. Information on production, use, transport and handling, environmental fate, and toxicity are reviewed.

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INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS:

BENZOTRIAZOLES

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Project Officer - Frank J. Letkiewicz

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EXECUTIVE SUMMARY

The current total production of benzotriazoles is estimated to be approximately 56 million pounds per year in the United States. Benzotriazoles are used in three main applications: to prevent the corrosion of metals, especially copper and materials containing copper (such as brass or bronze); to stabilize plastics and similar materials against the decomposition which would otherwise take place upon exposure of these materials to sunlight, fluorescent light, or other sources of ultraviolet radiation; and in photography, mainly as a constituent of films (antifoggant) to improve their photographic characteristics.

The majority of benzotriazoles produced go into anticorrosion applications. Typical applications include the protection of copper-containing parts (for which benzotriazole excels) by inclusion of benzotriazoles in automobile antifreeze solutions, in recirculating water systems such as power plant and commercial air conditioning cooling systems, and in coatings for the protection of copper alloys in architectural and decorative applications.

Approximately 20-30% of all benzotriazole production is used for the stabilization of plastics, paints, clear coatings, fabrics, and certain oil-based solvents against degradation on exposure to ultraviolet light. A variety of chemical derivatives (substitute at the 2-position) of benzotriazole are used in these applications, generally possessing chemical and possibly biological properties quite different from the parent compound.

The various photographic applications of benzotriazole consume only a small quantity of the total production (considerably less than one million pounds per year).

Only limited information is available on the possible release of benzotriazoles to the environment or the fate of benzotriazoles in the environment. Some 2-substituted benzotriazoles have been detected in ppb in river water and ppm in river sediment several miles downstream from a production plant. On the basis of their chemical properties, it is likely that the other benzotriazoles will be relatively stable and fairly persistent if released to the environment. Data on monitoring of the other benzotriazoles in the environment is unavailable.

Some benzotriazoles can inhibit the growth of bacterial cells and also cause mutations in some types of bacteria. This is significant because chemicals which are mutagenic frequently are carcinogenic as well. No studies of the potential carcinogenicity of benzotriazole have been completed yet, although work in this area is presently being carried out. It is therefore not now known what hazard, if any, benzotriazole may present with respect to the induction of tumors.

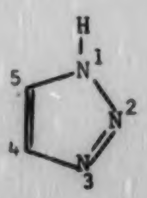
Animal studies have shown that benzotriazole dusts, if inhaled, may damage the lungs and severely interfere with breathing. The dust is also an explosion hazard. Benzotriazole dusts are not likely to be a hazard in current end use applications of these materials; dust hazard is most likely in places of manufacturing, packaging, and unpackaging of these chemicals. Current regulations do not set limits for benzotriazole dusts, but do limit the concentrations for some of the compounds used as ultraviolet light stabilizers in certain plastics consumed in food packaging.

I. Physical and Chemical Data

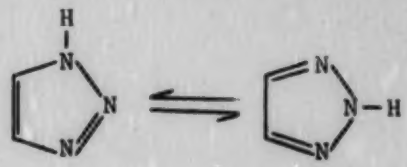
A. Structure and Properties

1. Chemical Structure

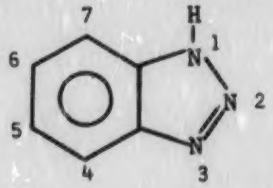
The benzotriazole compounds are derivatives of a five-member heterocyclic compound containing three nitrogen atoms and a vicinal pair of carbon atoms. The five-member heterocyclic compound is named 1_H_-1,2,3-triazole:



The 1_H_ refers to the position of the hydrogen atom associated with the nitrogen atoms; it may be on the #1 or #2 nitrogen atom. The 1_H_ and 2_H_ isomers are tautomers:

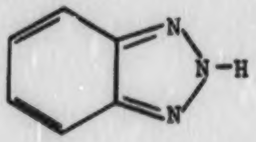


The numbering system of the molecules is indicated above. The numbers 1,2,3 in the nomenclature refer to the positions of the nitrogen atoms and thereby distinguish between the _v_ (vicinal) triazoles from the _s_ (symmetrical) triazoles. In the latter the nitrogen atoms are separated by a carbon atom between them and they are therefore named 1,2,4-triazoles. An ortho condensation of a benzene ring with a v-triazole ring describes the benzotriazole system (Boyer, 1961), the parent compound of which, and the major focus of this work, is the tautomer 1H-benzotriazole:

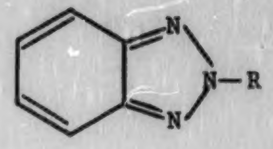


Other names commonly used for this compound are 1,2,3-benzotriazole and benzotriazole. Occasionally (especially in the older literature) the compound is referred to as azimidobenzene, benzene azoimide, or benzisotriazole. The accepted Chemical Abstracts numbering system for the atoms, as indicated above, follows from the numbering system for v-triazoles. In this review, the 1H structure is often referred to as simply benzotriazole.

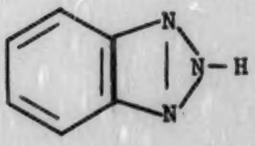
There exists the possibility of an alternate (tautomeric) structure for benzotriazole which is named 2H-benzotriazole (also referred to as pseudoazimidobenzene or 2,1,3-benzotriazole):



The 2H tautomeric structure is known mainly through its derivatives, which are of considerable theoretical interest because their exact structure is still a subject of controversy. Compounds of the type:



should be colored (but they are not) and exhibit quinoid properties (which they do not) (Benson and Savell, 1950). An alternative structure for 2H-benzotriazoles,



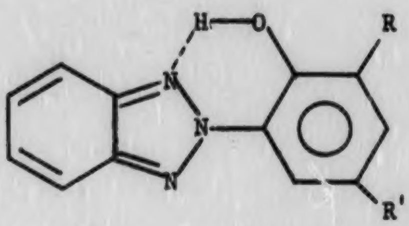
is an extremely strained arrangement which appears to be unlikely from geometric considerations alone (Benson and Savell, 1950). It has been suggested that the structure of 2H-benzotriazoles cannot be completely described exclusively on the basis of covalent bonds (Boyer, 1961).

Pure 2H-benzotriazole apparently has not been isolated, although numerous derivatives are stable (see, for example, Benson and Savell, 1950). X-ray studies have ruled out the possibility of the presence of symmetrical molecules in crystalline benzotriazole, suggesting the overwhelming predominance of the 1H tautomer in the solid state (Escande et al., 1974 a). This experimental evidence supports the earlier theoretical work of Kamiya (1970) who used the semiempirical Pariser-Parr-Pople self-consistent-field molecular orbital method to show that the ground energy states of the symmetrical 2H-benzotriazole molecule are higher than those of 1H-benzotriazole, implying the greater stability of the latter compound as compared to the former. Semiempirical complete-neglect-of-differential-overlap (CNDO) calculations of Escande et al. (1974 b) yielded results comparable to those of Kamiya (1970). When taken with spectral and dipole moment data (Mauret et al., 1974), the evidence supports the conclusion that, both in solution and the solid state, the 1H tautomer of benzotriazole represents the more stable and essentially exclusive molecular structure (Escande et al., 1974 b).

There are dozens of benzotriazole derivatives mentioned in the literature. Only three of these have achieved sufficient commercial status to merit mention by chemical name in the following publications:

Directory of Chemical Producers (SRI, 1975)
Synthetic Organic Chemicals 1974 (USITC, 1975)
Chemical Week 1976 Buyers' Guide (McGraw-Hill, 1975)
Chemical Buyers' Directory (Chem. Marketing Reporter, 1975)

These compounds are, in order of their commercial importance: 1H-benzotriazole, methylbenzotriazole (mixtures of 4- and 5-methyl isomers), and 5-chloro-1H-benzotriazole. In addition, there are at least eight other benzotriazole derivatives which have some commercial uses. The most important of these are members of the class 2-(2'-hydroxy-3',5'-alkylphenyl)-benzotriazole which have the structure:



The H bonding of the hydroxyl group keeps the molecule planar, thus allowing better conjugative overlap between the benzene ring and the benzotriazole system. Intramolecular hydrogen bonding therefore increases the stability of these compounds, which are marketed under the tradename Tinuvin (Ciba-Geigy, undated). The R groups on Tinuvins are H, CH_3-, *t*-butyl, and/or *t*-pentyl. The complete structures are shown in Table 1, along with the structures of other commercially significant benzotriazoles.

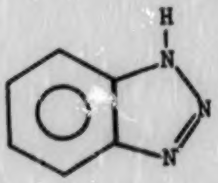
2. Mixtures

The Sherwin-Williams Chemical Company sells mixtures of 4-methyl-1*H*-benzotriazole and 5-methyl-1*H*-benzotriazole under the tradename Cobratec TT-100. This material, often referred to as "tolyltriazole," contains approximately equal amounts of the above two isomers, as well as small quantities of the 6- and 7-methyl isomers (Anon., undated). Cobratec TT-35-I is a 35% solution of the sodium salts of tolyltriazole mixtures. The methyl isomers in these salts presumably are in the same proportions to each other as in the solid tolyltriazole product.

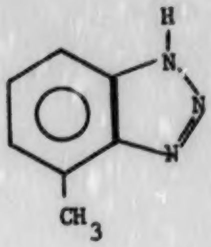
3. Physical Properties of the Pure Material

Benzotriazole and its derivatives listed in Table 2 are white to off-white or light yellow crystalline powders with melting points in the range 100-150°C (high for aromatic compounds of similar molecular weight) and generally high boiling or decomposition temperatures (ca. 300°C). In addition to their thermal stability, they are quite stable to electromagnetic radiation in the ultraviolet range. They dissipate absorbed ultraviolet energy as heat. The ultraviolet spectra of some of these compounds are shown in Figures 1, 2, and 3. The spectra are characterized by broad absorbance below 400 nm. The

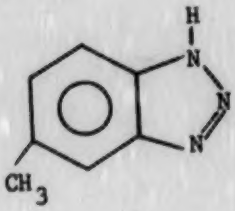
Table 1. Molecular Structure of Benzotriazoles



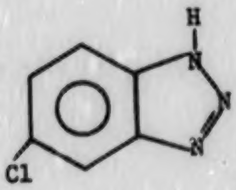
1*H*-benzotriazole



4-methyl-1*H*-benzotriazole

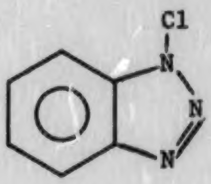


5-methyl-1*H*-benzotriazole

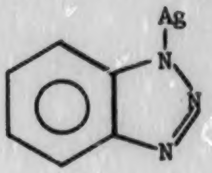


5-chloro-1*H*-benzotriazole

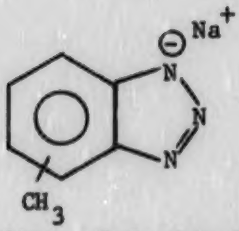
Table 1. Molecular Structure of Benzotriazoles (Cont'd)



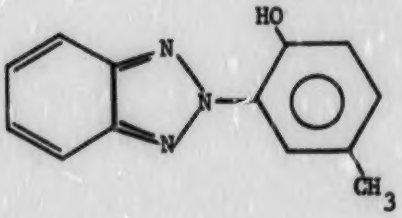
1-chlorobenzotriazole



silver benzotriazole

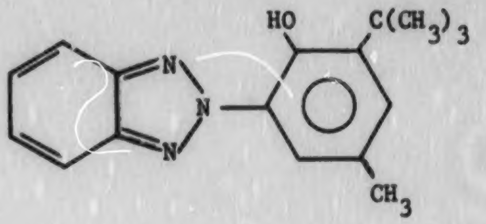


sodium tolyltriazole

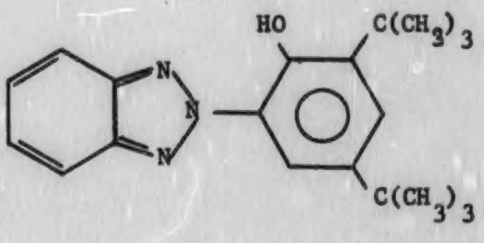


2-(2'-hydroxy-5'-methylphenyl)-benzotriazole

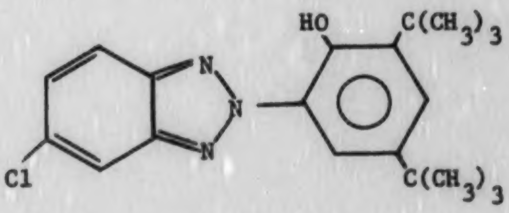
Table 1. Molecular Structure of Benzotriazoles (Cont'd)



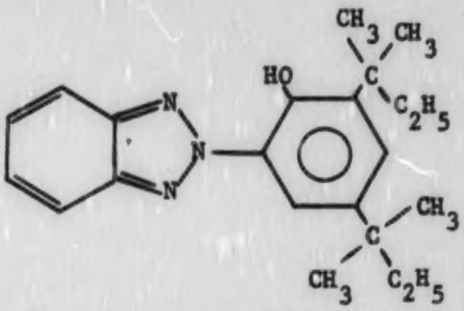
2-(3'-t-butyl-2'-hydroxy-5'-methylphenyl)-benzotriazole



2-(3',5'-di-t-butyl-2'-hydroxyphenyl)-benzotriazole



2-(3',5'-di-t-butyl-2'-hydroxyphenyl)-5-chlorobenzotriazole



2-(2-hydroxy-3',5'-di-t-pentylphenyl)-benzotriazole

Table 2. Physical Properties of Benzotriazole Compounds

	benzotriazole[1]	tolyltriazole[1]
Appearance	white powder	off-white granules
Odor	sweet	
Molecular Weight	119.12	133.16
Specific Gravity (25°C)	1.33	1.16
Flash Point °C (Tag Closed Cup)	> 150*	> 150*
Bulk Density (lbs./cu. ft.)	40, loose 55, packed	35-50, loose 40-45, packed
Melting Point, °C	98-99	
Vapor Pressure, torr (°C)	0.04 (20)	0.03 (50)
Boiling Point, °C (torr)	350 (760)	160 (2)
Dipole Moment, esu[4] (dioxane)	4.07×10^{-13}	
Heat of Combustion,[5] kcal/mole	794.97 ± 0.21	

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[1] Sherwin-Williams Company, product data sheets

[2] Fairmount Chemical Company, product data sheets

[3] Ciba-Geigy Corporation, product data sheets

[4] Benson and Savell (1950)

[5] Boyer (1961)

[6] Parish Chemical Company (1976), personal communication

[*] Sherwin-Williams Company, personal communication

Table 2. Physical Properties of Benzotriazole Compounds (Cont'd)

	5-chloro-1H-benzotriazole[2]	1-chlorobenzotriazole[6]
Appearance	white powder	
Odor		
Molecular Weight	153	153
Specific Gravity (25°C)		
Flash Point °C (Tag Closed Cup)		
Bulk Density (lbs./cu. ft.)		
Melting Point, C°	156-160	103
Vapor Pressure, torr (°C)		
Boiling Point, °C (torr)		
Dipole Moment, esu[4] (dioxane)		
Heat of Combustion,[5] kcal/mole		

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[1] Sherwin-Williams Company, product data sheets

[2] Fairmount Chemical Company, product data sheets

[3] Ciba-Geigy Corporation, product data sheets

[4] Benson and Savell (1950)

[5] Boyer (1961)

[6] Parish Chemical Company (1976), personal communication

Table 2. Physical Properties of Benzotriazole Compounds (Cont'd)

	2-(2'-hydroxy-5'-methylphenyl)benzotriazole[3]	2-(3',5'-di-*t*-butyl-2'-hydroxyphenyl)benzotriazole[3]
Appearance	crystalline powder	light yellow powder
Odor	none	none
Molecular Weight	225	301
Specific Gravity (25°C)	1.51	
Flash Point °C (Tag Closed Cup)		
Bulk Density (lbs./cu. ft.)		
Melting Point, C°	128-132	305-311
Vapor Pressure, torr (°C)	8×10^{-5} (60)	
Boiling Point, °C (torr)	225 (10)	
Dipole Moment, esu[4] (dioxane)		
Heat of Combustion,[5] kcal/mole		

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[1] Sherwin-Williams Company, product data sheets

[2] Fairmount Chemical Company, product data sheets

[3] Ciba-Geigy Corporation, product data sheets

[4] Benson and Savell (1950)

[5] Boyer (1961)

[6] Parish Chemical Company (1976), personal communication

Table 2. Physical Properties of Benzotriazole Compounds (Cont'd)

	2-(3',5'-di-t-butyl-2'-hydroxyphenyl)benzotriazole[3]	2-(2'-hydroxy-3',5'-di-t-pentyl)benzotriazole[3]
Appearance	light yellow powder	pale yellow powder
Odor	none	
Molecular Weight	301	358
Specific Gravity (25°C)		1.20
Flash Point °C (Tag Closed Cup)		
Bulk Density (lbs./cu. ft.)		
Melting Point, C°	140-141	154-158
Vapor Pressure, torr (°C)		
Boiling Point, °C (torr)		
Dipole Moment, esu[4] (dioxane)		
Heat of Combustion,[5] kcal/mole		

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[1] Sherwin-Williams Company, product data sheets

[2] Fairmount Chemical Company, product data sheets

[3] Ciba-Geigy Corporation, product data sheets

[4] Benson and Savell (1950)

[5] Boyer (1961)

[6] Parish Chemical Company (1976), personal communication

Table 2. Physical Properties of Benzotriazole Compounds (Cont'd)

	2-(3',5'-di-t-butyl-2'-hydroxyphenyl)-5-chlorobenzotriazole[3]
Appearance	off-white powder
Odor	
Molecular Weight	
Specific Gravity (25°C)	0.91
Flash Point °C (Tag Closed Cup)	
Bulk Density (lbs./cu. ft.)	
Melting Point, C°	81
Vapor Pressure, torr (°C)	10^{-3} (100)
Boiling Point, °C (torr)	
Dipole Moment, esu[4] (dioxane)	
Heat of Combustion,[5] kcal/mole	

[1] Sherwin-Williams Company, product data sheets

[2] Fairmount Chemical Company, product data sheets

[3] Ciba-Geigy Corporation, product data sheets

[4] Benson and Savell (1950)

[5] Toyer (1961)

[6] Parish Chemical Company (1976), personal communication

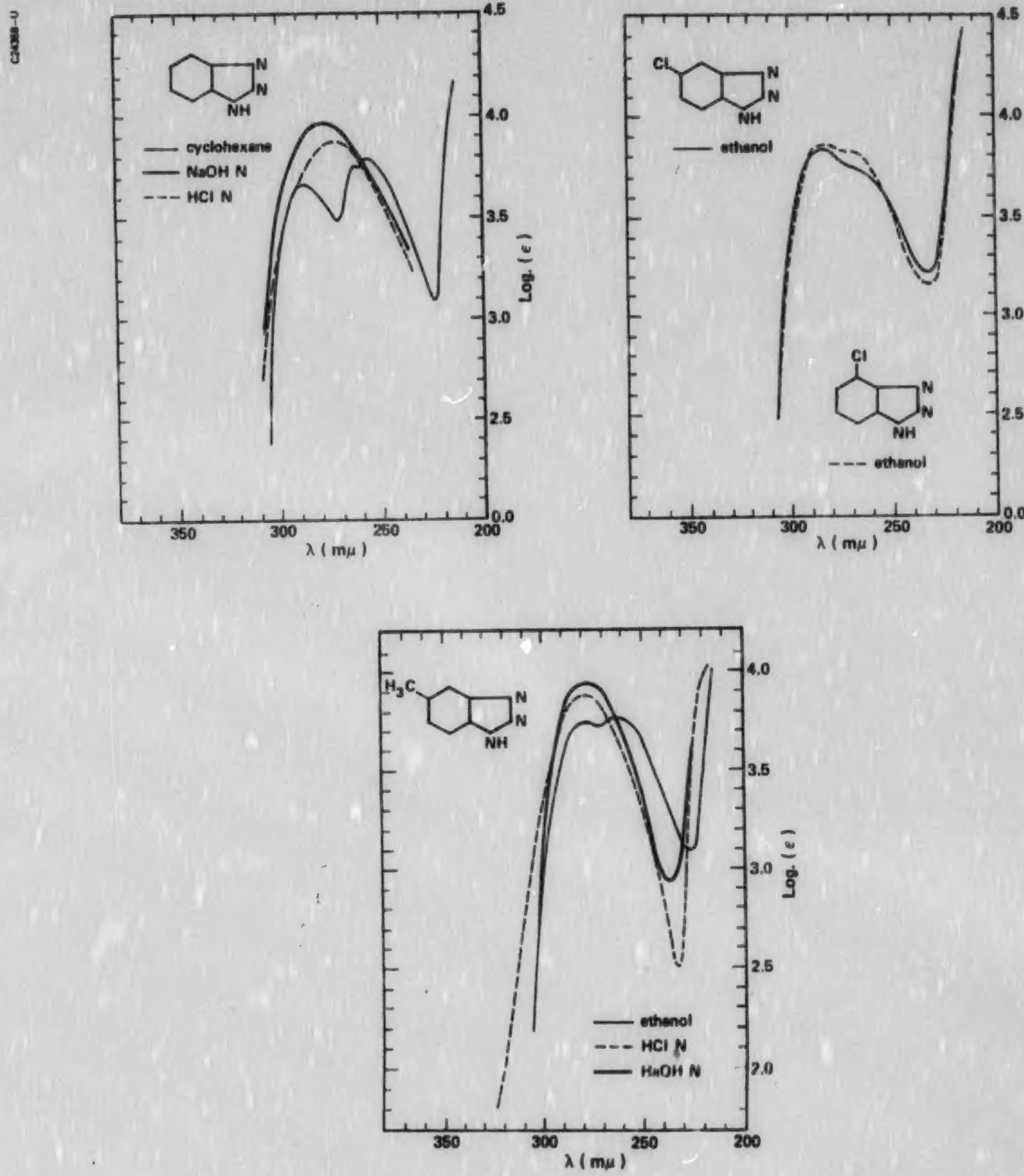


Figure 1. UV Absorption Spectra of Benzotriazole, 5-Chloro-1H-benzotriazole, and 5-Methyl-1H-benzotriazole (Dal Monte *et al.*, 1958)

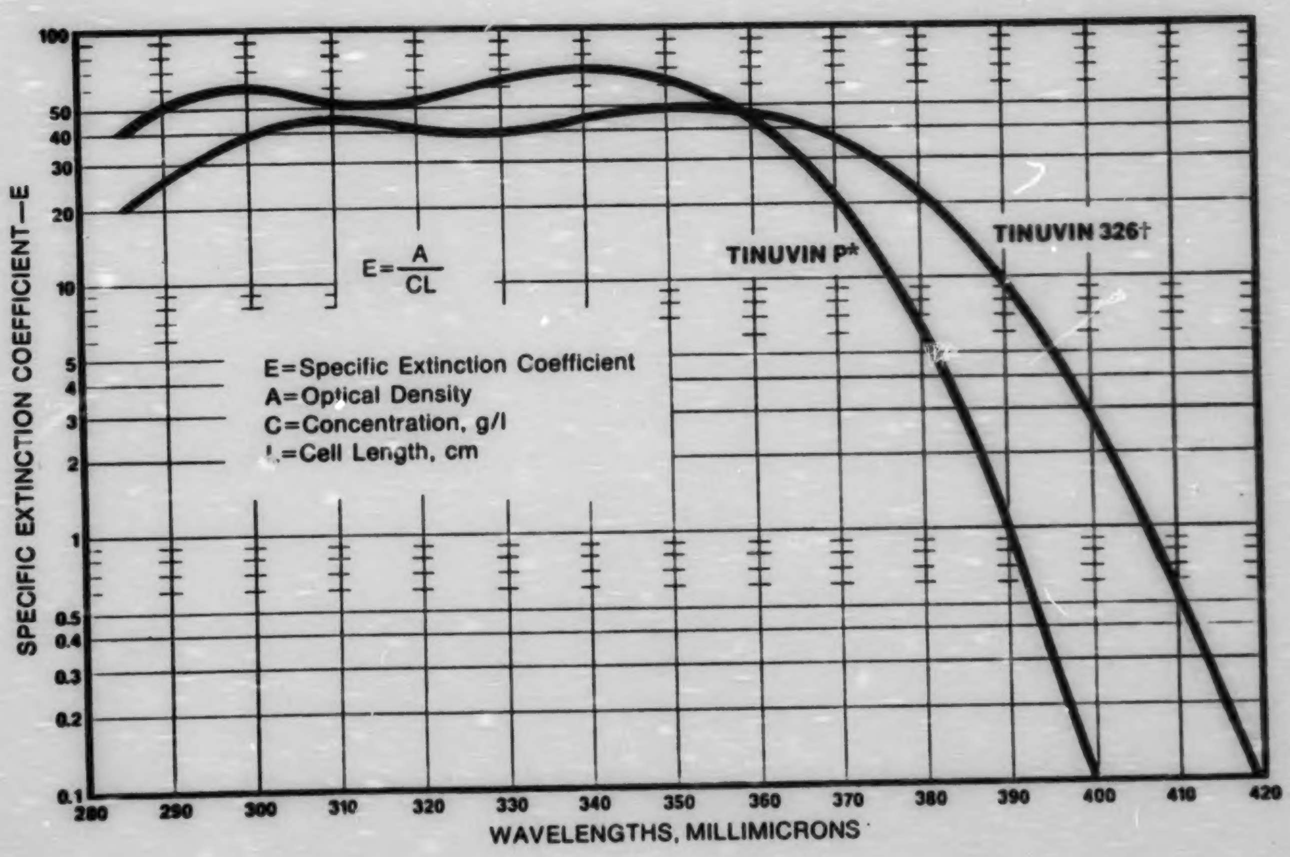
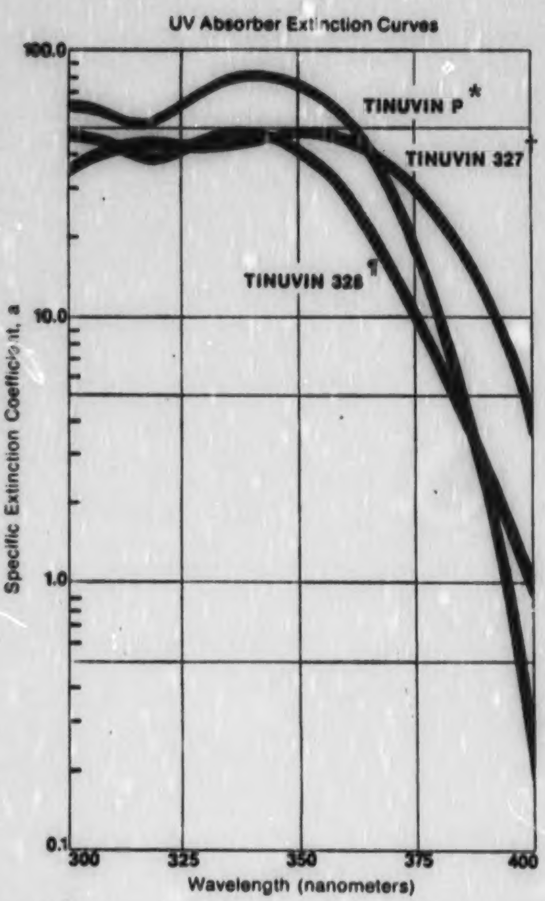


Figure 2. Specific Extinction Coefficient Spectra - Tinuvin 326* and Tinuvin P† in Chloroform (Ciba-Geigy, undated) (Reprinted with permission from the Ciba-Geigy Corp.)

* 2-(3'-t-butyl-2'-hydroxy-5'-methylphenyl)-benzotriazole

† 2-(2'-hydroxy-5'-methylphenyl)-benzotriazole



$a = \frac{A}{bc}$

a = Extinction Coefficient
c = Conc. in g/liter
b = Path Length = 1 cm

* 2-(2'-hydroxy-5'-methylphenyl)-benzotriazole
† 2-(3',5'-di-t-butyl-2'-hydroxyphenyl)-benzotriazole
¶ 2-(3',5'-di-t-pentyl-2'-hydroxyphenyl)-benzotriazole

Figure 3. UV Absorption Spectra of Several 2-(3',5'-Alkyl-2'-hydroxyphenyl)-benzotriazoles (Ciba-Geigy Corp., undated)

(Reprinted with permission from the Ciba-Geigy Corp.)

specific extinction coefficients at absorption maxima for two of the 2-(2'-hydroxyphenyl)-benzotriazoles are listed in Table 3. The 2-(2'-hydroxyphenyl)-benzotriazoles tend to absorb at longer wavelengths than other benzotriazoles, hence their pale yellow color when pure.

Table 4 lists solubility data for benzotriazole and its derivatives. They range from insoluble to somewhat soluble in water and nonpolar solvents, to soluble in most organic polar oxygenated solvents. The solubility of benzotriazole in water varies widely with temperature, as shown in Figure 4; it can be as high as 20% (w/v), but is less than 2% (w/v) at temperatures below 30°C. The water solubility of benzotriazole is high enough to be a factor in the transport of this material in the environment. The solubility of the 2-(2'-hydroxyphenyl)-benzotriazoles (Tinuvins) in a given solvent depends to a large extent on the particular alkyl groups on the 3' and 5' positions. The solubility of Tinuvin 328 (with t-pentyl phenyl substituents) in esters and (nonpolar) xylene is two to four times the solubility of Tinuvin P (with a single methyl substituent on the phenyl) or Tinuvin 326 (with methyl and t-butyl substituents). The water solubility of 2-(2'-hydroxyphenyl)-benzotriazoles is lower than expected for similar molecules which are not capable of internal hydrogen bonding; Tinuvins are, in fact, insoluble in water. Solubility data was not available for compounds not listed in the tables.

4. Physical Properties of Commercial Material

Some commercial applications require a highly purified benzotriazole product, whereas technical grade material will do for others. Benzotriazole and 5-chloro-1H-benzotriazole which are labeled "photo grade" are examples of high purity material whose physical properties are as described in

Table 3. Specific Extinction Coefficients of Several 2-(3',5'-alkyl-2'-hydroxyphenyl)-benzotriazoles (Ciba-Geigy Corp., undated)

	2-(2'-hydroxy-5'-methylphenyl)-benzotriazole		2-(3'-t-butyl-2'-hydroxy-5'-methylphenyl)-benzotriazole		2-(3',5'-di-t-butyl-2'-hydroxyphenyl)-benzotriazole	
	$\lambda_{max.}$	Sp. Ext. Coeff.	$\lambda_{max.}$	Sp. Ext. Coeff.	$\lambda_{max.}$	Sp. Ext. Coeff.
chloroform	312	46	298	61	315	42
	350	50	340	70	352	47
methanol	298	47	296	65		
	343	51	345	66		

Table 4. Solubilities of Benzotriazole Compounds

	BT	TTZ	Cl-BT	Tin-P	Tin-326	Tin-327	Tin-328
Water	1.98	0.55	slight	0	0	0	0
Water, 60°C	7.4	1.8	moderate				
Methanol	71.[illegible]	71.6	soluble				
1-Methoxy-2-propanol	55.0	52.3					
Isopropanol	53.9	52.9					
Ethylene glycol	50.7	45.6					
Polyethylene glycol	47.7	41.1					
Methyl ethyl ketone	46.1	41.4		10 gm/100 gm	2.9	4	24 gm/100 gm
Heptanol	34.6	35.9					
Benzene	1.3	1.3					
White mineral oil	0.004	0.008					
Tetrachloroethylene	0.06	0.13					
Turbine oil	0.01	0.014					
Ethanol (abs.)	soluble			0.3		0.3	
Ethyl acetate				3.5	2.5	6	20 gm/100 gm
Methyl methacrylate				5	4.9	14	
Petroleum ether					1.8		
Styrene				7.2	12.6	14	
Toluene				6.0		16	
Xylene				7 gm/100 gm		15	44 gm/100 gm
Mineral spirits				1.5		5	14 gm/100 gm
n-Butyl acetate				4 gm/100 gm		10 gm/100 gm	28 gm/100 gm
Cyclohexane						8	
Hexane						3	
Dioctyl phthalate				2.5		3	
Acetone				2.5			
Methyl cellosolve				1.7			

KEY:	
BT	Benzotriazole
TTZ	Tolyltriazole
	(Data for the above in wt.% @25°C) (Korpics, 1974 a)
Cl-BT	5-Chloro-1H-benzotriazole (Fairmount Chemical Co., product data sheet)
Tin-P	2-(2'-hydroxy-5'-methylphenyl) benzotriazole
Tin-326	2-(3'-t-butyl-2'-hydroxy-5'-methylphenyl)-benzotriazole
Tin-327	2-(3',5'-di-t-butyl-2'-hydroxyphenyl)-benzotriazole
	(Data for the above in gm/100 ml solvent, except where indicated otherwise) (Ciba-Geigy Co., undated)
Tin-328	2-(2'-hydroxy-3',5'-di-t-pentylphenyl)-benzotriazole (Ciba-Geigy Co., undated)

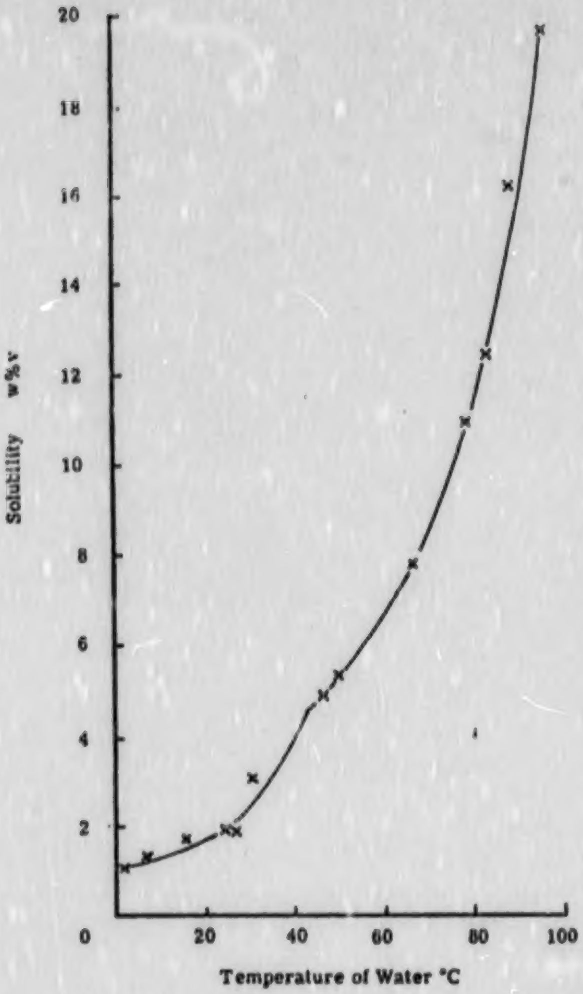


Figure 4. Effect of Temperature on the Solubility of 1H-Benzotriazole in Water (Walker, 1970)

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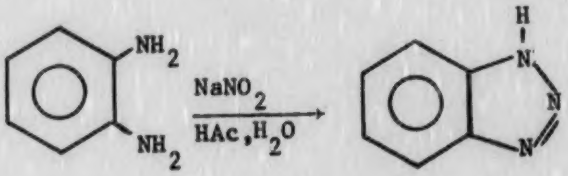
the previous section. Applications such as corrosion inhibition utilize technical grade chemicals or mixtures of benzotriazoles. Tolyltriazole, for example, is a mixture of the 4-, 5-, 6-, and 7-methyl-1H-benzotriazole isomers. In the application for which this material is intended, the efficacy of the mixture is the same as any single pure isomer would be. Certain physical properties, such as melting point, may vary for the mixture from the pure material and from batch to batch of the mixture. The manufacturer's specifications are given in Table 5 for benzotriazole commercial chemicals where the specifications supplement or are different from the data in Table 2.

5. Principal Contaminants of the Commercial Product

It is likely that the most widely used commercial methods for large scale preparation of benzotriazole are those suggested by Levy (1966) and Long (1971) (which are adaptable to the preparation of certain derivatives of benzotriazole as well), in which 1,2-diaminobenzene (o-phenylenediamine) is diazotized with sodium nitrite in the presence of acetic acid (HAc) in an aqueous medium:



Time, temperature, and pH factors all affect the yield of the reaction. The benzotriazole forms as an oily liquid which is separated and purified in a complex series of steps including water washing, water evaporation, distillation under reduced pressure, condensation, and solidification. Details of the

Table 5. Commercial Specifications for Some Benzotriazole Compounds

	Benzotriazole,[1] photo grade	Benzotriazole,[1] technical	Benzotriazole,[2] photo grade	Benzotriazole,[2] technical	Tolyltriazole,[2] technical
Assay, %	99.0, min.	95, min.	98, min.	98, min.	99, min.
Melting Point, °C	96-100		98-99	94-99	
Ash, % max.	0.01			0.5	0.5
Loss on Drying @70°C, % max.	0.5	1	0.5	0.5	0.5
Cl^-, Br^-, & I^-	to pass ASA test				50 ppm max. Cl^-
Solubility in H_2O	1% sol. is clear	2% @25°C	[illegible] sol. is clear		
Solubility in Absolute Ethanol	1% sol. is clear				
Solubility in 10% NaOH	1% sol. is clear				
Free Amine, % max.					0.2

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[1] Fairmount Chemical Company, Newark, New Jersey

[2] Sherwin-Williams Chemical Company, Cleveland, Ohio

processes are given in Section II-A-3. Most of the product nominally lost in the purification steps (i.e., dissolved in the wash water) is recovered and recycled, resulting in a high overall yield of 97%. The product is also high in purity. Sherwin-Williams Co. (undated), for example, specified 98% minimum purity for technical grade benzotriazole, and 99% minimum purity for technical grade tolyltriazole. The typical assays for these products yield a purity of 99.5%. Moisture and ash account for 0.5-1.0% of the remainder. The tolyltriazole product can have up to 0.2% free amine (possibly aniline) and 50 ppm chloride ion. One important commercial test for the purity of these products is based on their nearly colorless (white) appearance when pure. The oxidation products of the benzotriazoles are dark in color; hence, the darker the material (in solution), the more impurities are present. The major impurities are likely to be oxidation products of the starting material, 1,2-diaminobenzene, including o-nitroaniline, 1,2-dinitrobenzene, nitrosamine intermediates, and possibly polyamines. The extent of the side reactions which produce these undesired contaminants is controlled by reaction conditions (Long, 1971). These impurities are most tolerable in benzotriazoles intended for anticorrosion applications, less so in benzotriazoles intended for use as ultraviolet absorbers (especially in plastics where color imparted by an additive, even in small quantities, is usually undesirable), and least tolerable in benzotriazole intended for photographic applications because the contaminants are usually photographically active. "Photograde" benzotriazole is the highest purity commercially available grade, essentially free of colored contaminants.

In summary, benzotriazole commercial chemicals, even the technical grade, are high purity materials as supplied. The principal contaminants are likely to be moisture, ash, and some oxidation products of the 1,2-diaminobenzene starting material, which impart a dark color to benzotriazole and are measured by standard colorimetric tests.

B. Chemistry

1. Reactions Involved in Uses

The major uses to which benzotriazoles are put, namely as anticorrosion agents, plastics stabilizers, and photographic antifoggants, depend on physical and chemical properties which are a unique combination of chemical versatility and stability. Stability is a key concept in benzotriazole chemistry. Although the molecule will undergo, under the proper conditions, a wide variety of reactions (including aryl and N-halogenation, nitration, hydroxylation, acylation, alkylation, oxidation, hydrogenation, condensation, and arylation, to name a few), the integrity of the triazole ring is almost never compromised (Sherwin-Williams Co., undated). Benzotriazole compounds react readily to form stable metal complexes which are capable of protecting the metal (particularly copper) from further chemical attack. Although practically colorless to the human eye, benzotriazole compounds absorb over a broad range in the ultraviolet region of the electromagnetic spectrum and dissipate the absorbed energy, usually not by bond breaking and free radical formation, but by harmless physical vibration and the emission of heat. Benzotriazole compounds are therefore capable of protecting less stable molecules from degradation on exposure to ultraviolet radiation. It is, then, the combination of chemical versatility which allows modifying solubility, absorption spectra, compatibility with plastics, etc., of benzotriazoles on the one hand, and the relative physical and chemical stability of the benzotriazoles on the other, which chiefly characterizes benzotriazole and its derivatives in their major commercial applications. The chemistry of these applications is considered in detail below.

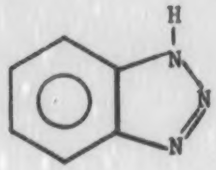
a. Anticorrosion

Benzotriazole's anticorrosion properties were recognized long before the mode of protection began to be understood. One of the earliest efforts to elucidate the mode of protection involved a study of the effect of benzotriazole on copper electrodeposits (Prail and Shreir, 1961). It was recognized that the association of the benzotriazole and copper was not simply that of a protective physical coating adsorbed on the metal surface, but a more intimate chemical association described as a "cuprous benzotriazolate" complex. It was also suggested (erroneously, as it turned out) that in order for benzotriazole to be effective in protecting copper, it must be "released from the metal complex during the corrosion process."

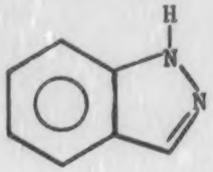
On the basis of electrochemical investigations, Dugdale and Cotton (1963) concluded that prevention of copper corrosion results from the formation of a copper-benzotriazole complex which acts as a cathodic inhibitor for the oxidative reaction, assisted by the physical barrier the complex presents on the metal surface.

The particular features of the benzotriazole molecule which make it an excellent anticorrosion agent were reported by Cotton and Scholes (1967) in a study of copper complexes with the compounds listed in Table 6. Neither indole nor 1-methylbenzotriazole formed insoluble complexes with either cupric or cuprous ions. Consequently, physical protection is not possible with these materials; apparently both the 1H hydrogen atom and at least two nitrogen atoms are needed in the five-member ring to obtain anticorrosion properties. Benzimidazole (a weak base) formed a dark red, insoluble complex with copper, but failed to protect copper against corrosion, suggesting

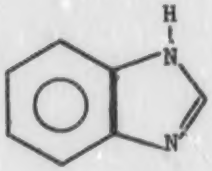
Table 6. Compounds Used in the Study of Cotton and Scholes (1967)



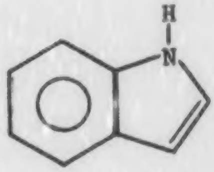
1H-benzotriazole



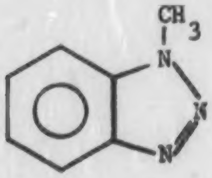
indazole



benzimidazole



indole



1-methylbenzotriazole

that the two nitrogens in the ring must be adjacent to each other. Both indazole (a neutral compound) and benzotriazole (a weak acid) formed dark green, insoluble complexes and both compounds protected copper from tarnish. However, copper treated with benzotriazole could be washed with chloroform and still retain its resistance to tarnish, whereas indazole-treated specimens did not retain their resistance to corrosion after rinsing in chloroform. Modifications to the benzene ring have little effect on the anticorrosion properties of benzotriazole. Thus, the following compounds behave similarly with respect to preventing the corrosion of copper: benzotriazole, 4-, 5-, 6-, or 7-methylbenzotriazole, 4-, 5-, 6-, or 7-chlorobenzotriazole, and napthotriazole. However, the six-member aromatic ring appears essential, because five-member heterocycles (and their derivatives), such as imidazole, 1,2,4-triazole, and pyrazole, showed little or no inhibitive properties.

In 1969 Bonora _et al_. confirmed the presence of a protective layer on copper sheets treated with benzotriazole and suggested that oxygen plays a part in the formation of the layer. Moreover, it was shown that benzotriazole inhibits both anodic and cathodic polarization on copper in saline solution, whereas another commonly used anticorrosion agent, 2-mercaptobenzothiazole, inhibits only the cathodic polarization.

Poling (1970) used infrared reflectance measurements to determine the structure of the copper-benzotriazole complex formed on copper sheets in neutral solution. This was the first attempt to examine the nature of the complex _in situ_ as opposed to the complex which precipitates from a solution of cuprous ions when benzotriazole solution is added. Polymeric films of copper-benzotriazole complex formed in acidic (pH = 3) aqueous solutions of sodium chloride were found to be from 2300-5000 Å thick on the surface of the sheets of copper, in contrast to the monomolecular film (ca. 50 Å thick) reported by Cotton and Scholes (1967). The films were inert to the common organic solvents listed in Table 7. They were attacked by pyridine, formic acid, and disodium (ethylenedinitrilo)-tetraacetic acid. Prolonged heating in air at 140°C had little effect on the films. After heating for two hours at 250°C, however, a film which was 2300 Å thick prior to heating evaporated to a thickness of 400 Å. No changes were noted in the infrared spectrum of the residual film. The rate of oxidation of the underlying copper was reduced significantly by the presence of the films as deduced from relative intensities of Cu_2O spectra. The mechanism of growth of the polymeric films of Cu(I)-benzotriazole below the initial layer was attributed to the diffusion of cuprous ions through the surface of the films, which was encouraged by the presence of a corrosive solution at the surface (and also polarization of the copper samples). In addition, the films formed a protective barrier which inhibited oxygen transport to the copper below the surface.

In spite of the new information, the exact nature of the polymer film was yet to be determined. Angely *et al*. (1971) took a step in that direction with the demonstration of a 2:1 ratio between the number of copper atoms and benzotriazole molecules in the films. Electrochemical techniques led to the quantification of the enthalpy of the reaction between benzotriazole and the copper surface, which is 11 kcal/mole. The adsorption energy was shown to exceed the desorption energy by 9.4 kcal/mole, confirming the irreversibility of the reaction between copper and benzotriazole.

In 1973 Mansfield and Smith resolved the discrepancy between the findings of Cotton that the copper-benzotriazole layer is about 40 Å thick (Dugdale and Cotton, 1963; Cotton and Scholes, 1967) and Poling (1970) who found

Table 7. Effect of Solvents on Copper-Benzotriazole Complex on Copper Sheets (Poling, 1970)

Inert To	Slowly Dissolved By
heptane	pyridine
benzene (hot or cold)	formic acid
carbon tetrachloride	disodium (ethylenedinitrilo)-tetraacetic acid
chloroform	
ethyl ether	
acetone	
methyl isobutyl ketone	
ethyl acetate	
acetonitrile	
dimethylformamide	
nitromethane	

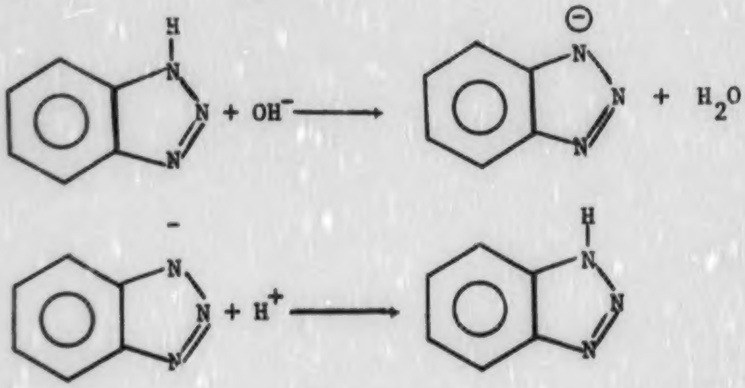
it to be several thousand angstroms thick. The thickness of the complex layer was shown to be a function of the pH at which it is formed. At the low pH's Poling used, a thick porous salt film forms. This thick film does not form at or near neutral pH's. The salt film can easily be wiped off, but the underlying film (60-140 Å) cannot.

Benzotriazole generally causes a reduction in the pH of solutions to which it is added. This effect has been attributed to minimization of the cathodic reactions which tends to increase pH (Walker, 1970):

$$2H^+ + 2e^- \rightarrow H_2$$

$$2H_2O + O_2 + 4e^- \rightarrow 4OH^-$$

At the same time, benzotriazole tends to buffer the solution in the following manner:



Using X-ray photoelectron spectroscopy, Roberts (1974) determined that the rate of adsorption of benzotriazole depends not only on pH but also on the nature of the surface of the copper, a cuprous oxide surface adsorbing benzotriazole faster than a cupric oxide surface. The Cu^+-benzotriazole complex which forms is at least ∿15±7 Å thick and gradually oxidizes to Cu^{+2}-benzotriazole. Several possible structures for the complex have been suggested and are shown in Figure 5.

Ogle and Poling (1975) confirmed Roberts's findings that the composition of the protective surface film is primarily Cu^{+}-benzotriazole. In acidic solutions, in which Cu_2O is unstable, the film network consists of acircular crystals of Cu^{+}-benzotriazole several thousand angstroms thick. Electrochemical polarization curves indicate that protection is afforded mainly via the physical barrier presented by the film. Excess benzotriazole in the corrosive environment prolongs the protection due to the possibility of repair to the physical defects which may develop in the film barrier.

In summary, the evidence indicates that benzotriazole forms a thin, highly stable, monomolecular polymeric film on copper surfaces consisting mainly of cuprous benzotriazole monomeric units. The film is thermally and chemically quite stable. At low pH's the film may be overcoated with a porous metal-benzotriazole salt layer.

b. Photostabilization

The Tinuvin compounds (2-(2'-hydroxyphenyl)-benzotriazoles) are photochemically stable materials capable of adsorption of electromagnetic radiation in the ultraviolet range between approximately 300-400 nm, and dissipation of the energy as heat. They are therefore useful in preventing the decomposition of substrates which are otherwise degraded by exposure to ultraviolet light from the sun and fluorescent lamps. Typical substrates include polyolefins, clear coatings, and paints. Intramolecular hydrogen bonding in the Tinuvins is the key to their effectiveness as UV stabilizers. This effectiveness is diminished significantly if the hydroxyl hydrogen is replaced by an

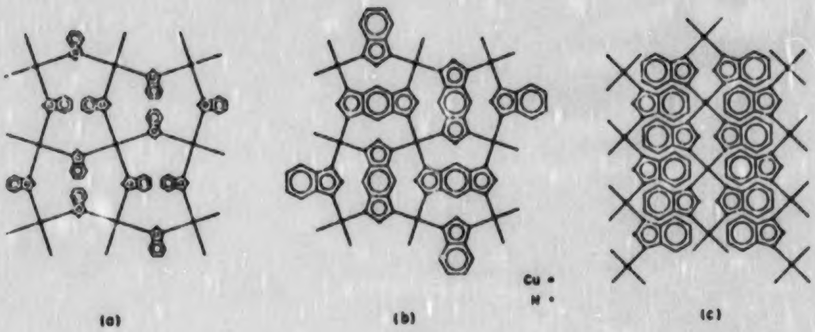


Figure 5. Suggested Structures for Cuprous-Benzotriazole Complex Polymers (Roberts, 1974)

Note: Structure (b) is structure (a) with the atoms placed in proportion to their relative inter-atomic distances. Thus, structure (b) indicates overlapping of benzene rings.

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alkyl or acyl group (Rothstein, 1968). The physical relationship the protecting compound has with the substrate also determines its effectiveness. In polypropylene, for example, dissolved Tinuvins are accumulated mainly in noncrystalline regions, which happen to require the most protection against photochemical decomposition (Frank and Lehner, 1970). In addition to the primary site of accumulation of the UV stabilizer, its relation to the substrate with respect to migration is an important factor in the length of time protection is afforded. The concentration of Tinuvins tends to be more stable in polypropylene films than other stabilizers (Vink, 1973). However, the vapor pressure of most Tinuvins is so high that after eventual diffusion of the molecule to the surface of the substrate, evaporation takes place almost immediately (Durmis _et al._, 1975). The loss of stabilizer is thus a function of its diffusion rate in the substrate even for those stabilizers with relatively low vapor pressures, and, of course, increases with increasing temperature. It has been shown that a linear phenyl substituent reduces the diffusion of the stabilizer more effectively than a branched substituent (Durmis _et al._, 1975). Application of UV stabilizing benzotriazoles to specific substrates is discussed in Section II-B-1.

c. Photographic Antifoggant

Photographic emulsions contain silver halide grains which, upon exposure to light, become semipermanently excited. This excitation or "memory" manifests itself in their increased electrophilicity, that is, greater reducibility than unexposed crystals. Hence, in the presence of mild reducing (developing) agents such as _p_-aminophenol or hydroquinone, colorless silver halide grains which have been exposed to light are reduced to black grains of silver metal:

$$\underset{\text{colorless}}{Ag^+Br^-} + e^- \rightarrow \underset{\text{black}}{Ag0} + Br^-$$

The remaining silver ions which were unexposed to light and therefore not reduced, are removed from the emulsion by complexation with, typically, thiosulfate ions, which react rapidly with silver ions to form a very stable water soluble complex; at the same time thiosulfate is relatively unreactive towards the silver atoms which make up the developed, visible photographic image:

$$Ag^{+} + 2S_2O_3^{-2} \rightarrow Ag(S_2O_3)_2^{-3}$$

Unfortunately, even if they have not been exposed to light, all photographic emulsions tend to form metallic silver on treatment with reducing agents. This unexposed but developed image is known as "fog" (John and Field, 1963). Because it reduces the effective dynamic range of shading (contrast) of the film as well as its relative sensitivity to light (speed), fog is considered undesirable. Fog is analogous to "noise" in electronic parlance where design parameters are usually optimized to give the highest signal-to-noise ratio possible. Photographers seek to achieve the highest possible minimum image density-to-fog density ratio.

The causes of fog are complex and varied. They include manufacturing conditions, storage conditions of the film before and after exposure, nature of the developing agents, pO_2 of the developer, contamination of the film by foreign airborne substances, such as H_2S, the presence of silver halide solvents in the developer (i.e., thiosulfate or thiocyanate ions), and exposure of the film to X-rays, gamma rays, or a weak source of light prior to or during development.

There are two chemical approaches generally taken to minimize fog. One, almost universally practiced, is to add Br^- to the developer

(John and Field, 1963). Since Br^- is formed during development (see equation above), the Law of Mass Action predicts that excess bromide ion will retard development. Retarding the formation of the image and fog by the same amount has the effect of reducing the fog level significantly, much as negative feedback loops in electronic amplifiers reduce noise levels while simultaneously sacrificing some gain in signal level. Bromide ion is therefore more correctly viewed as a development restrainer than an antifoggant. The second chemical approach to fog reduction is to employ a substance which reduces fog levels while having little effect on image density. Such substances are said to satisfy the following relation (Mees and James, 1971), and benzotriazole is one of the more commonly employed among them:

$$\frac{K_{AgBr}}{K_{AgZ}} \times \frac{a_{Z^-}}{a_{Br^-}} > 1$$

where the K's are solubility product constants of AgBr and the silver salt of Z, the antifoggant, and a_{Br^-} and a_{Z^-} are the activities of these ions in the developer solution. Thus, for $K_{AgBr} = 7.7 \times 10^{-13}$ (Weast, 1967), $K_{AgBt} = 2.2 \times 10^{-14}$ (Havir, 1967), and assuming the activities ≈ concentrations of Br^- and benzotriazole ion for typical formulations in which $\{Br^-\} \approx 10^{-2}$ and $\{Bt^-\} \approx 10^{-5}$, then the value of the expression above ≈ 4. Benzotriazole is an effective antifoggant in relatively small concentrations (i.e., ca. 10^{-5} M (Battaglia, 1970)) so that its activity as an antifoggant is not entirely attributable to a decrease in effective $\{Ag^+\}$ due to the formation of a relatively insoluble silver benzotriazole compound on the surface of a silver halide crystal

(Sahyun, 1970; Mees and James, 1971). Apparently, some type of kinetic process, such as activation energy, is also a factor (Battaglia, 1970).

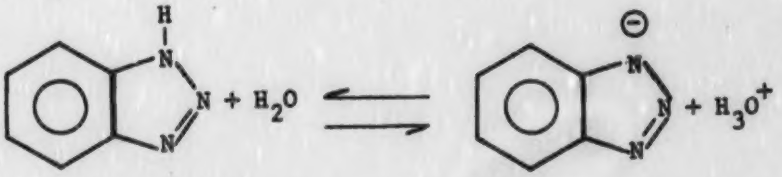
Benzotriazole is known to react with free radicals (Broyde, 1970). Although it is not certain that free radicals are present in fog centers, it has been shown that benzotriazole does react selectively with fog center sites rather than with the silver halide grain surface in general (Sahyun, 1971). Consequently, benzotriazole would be expected to supress fog arising from a free radical source.

On the other hand, it has also been suggested that benzotriazole adsorbed on the surface of silver halide grains interferes with desorption of bromide ion, which is necessary to maintain crystal stoichiometry during reduction (Sahyun, 1974). This restraining action would reduce both image and fog density.

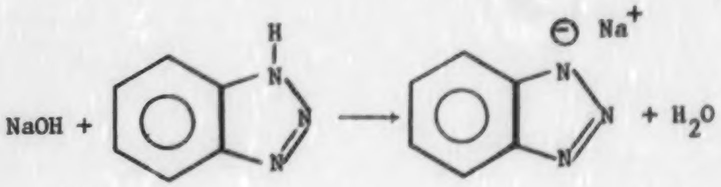
In summary, it is clear that the question of the exact mode of action of this and other similar antifoggants is far from settled.

2. Hydrolysis

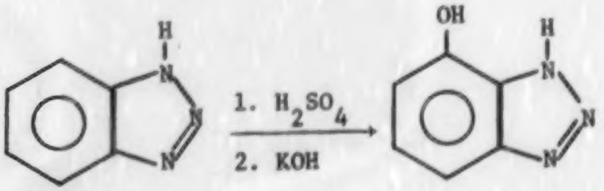
Benzotriazole, a weak acid, is somewhat soluble in water (see Section I-A-3). Many of its derivatives, such as the 2-(2'-hydroxyphenyl)-benzotriazoles, are not soluble in water to any appreciable extent. Solutions of benzotriazole in pure water are acidic because of the reaction:



The pK_a for this reaction is 8.2 (Boyer, 1961). Benzotriazole becomes a stronger acid as chlorine is substituted on the benzene ring (see Table 8). The insolubility of the 1- and 2-alkyl substituted benzotriazoles is attributable to the fact that these compounds cannot hydrolyze as does benzotriazole in the above reaction. The above equation also suggests that benzotriazole will be less soluble in solutions of pH < 7 (such as rainwater) and more soluble in solutions of pH > 7 (such as seawater) than in distilled water. Benzotriazole reacts with solutions of alkali metal hydroxides producing soluble alkali salts:



Treatment of benzotriazole with an aqueous acid followed by alkali causes hydroxylation (Sherwin-Williams Co., undated):



This reaction is unlikely to take place in the environment.

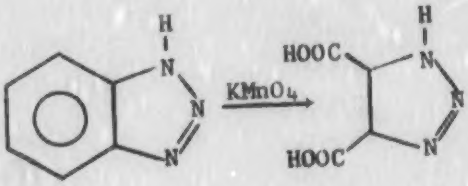
In the presence of strong acids, benzotriazole behaves as a Lewis base. Therefore, benzotriazole, 5-chlorobenzotriazole, and 2-methylbenzotriazole are soluble in aqua regia, but 4,5,6,7-tetrachlorobenzotriazole, a much stronger acid than the others, is not soluble (Boyer, 1961).

Table 8. Relative Acid Strength of Some Benzotriazole Compounds

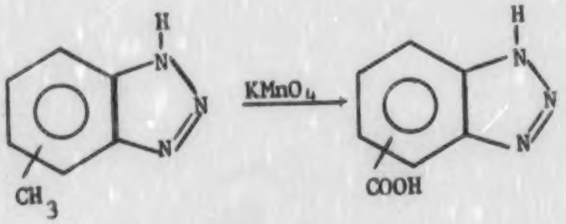
	pKa	Solvent	Source
1*H*-Benzotriazole	9.1	50% aq. ethanol	Büchel and Draber, 1969
	8.2	Water	Boyer, 1961
5-Chloro-1*H*-benzotriazole	8.0	50% aq. ethanol	Büchel and Draber, 1969
	7.7	Water	Boyer, 1961
4-Bromo-1*H*-benzotriazole	7.9	50% aq. ethanol	Büchel and Draber, 1969
5-Nitro-1*H*-benzotriazole	6.5	50% aq. ethanol	Büchel and Draber, 1969
4,5,6,7-Tetrachloro-1*H*-benzotriazole	5.5	Water	Boyer, 1961
	5.2	50% aq. ethanol	Büchel and Draber, 1969
2-(2'-Hydroxy-5'-methylphenyl)-benzotriazole	-1.068	80% aq. dioxane	Ciba-Geigy Corp., 1972
2-(3'-*t*-Butyl-2'-hydroxyphenyl)-benzotriazole	-1.114	80% aq. dioxane	Ciba-Geigy Corp., 1972

3. Oxidation

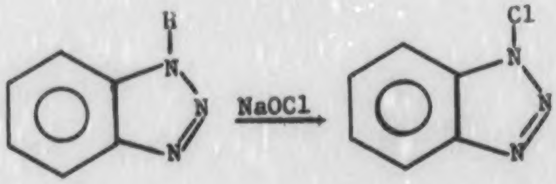
The triazole ring is extremely resistant to oxidation (Sherwin-Williams Co., undated). The benzene ring is relatively stable, but will undergo oxidation under strenuous conditions:



Alkyl substituents, if present, are oxidized in preference to the aromatic ring. Thus, for tolyltriazole:



Benzotriazole will undergo substitution rather than oxidation in the presence of certain strong oxidizing agents:



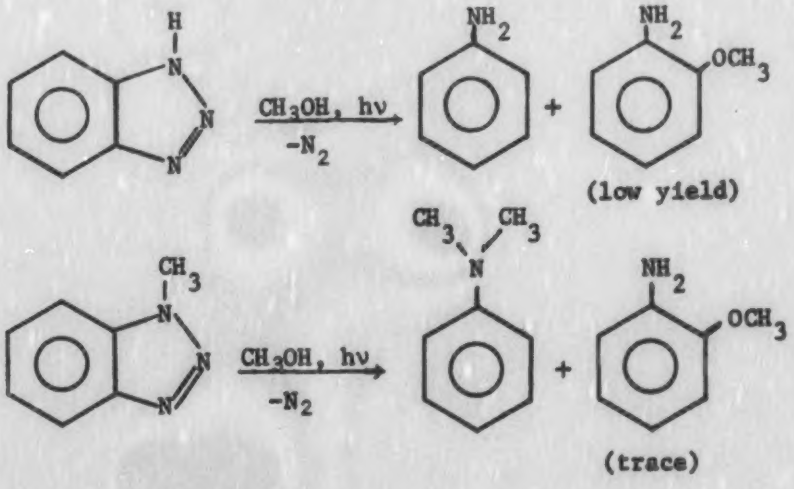
The pure solid 1-chlorobenzotriazole is considered an unstable compound, known to have burst into flame while being packaged (Hopps, 1971).

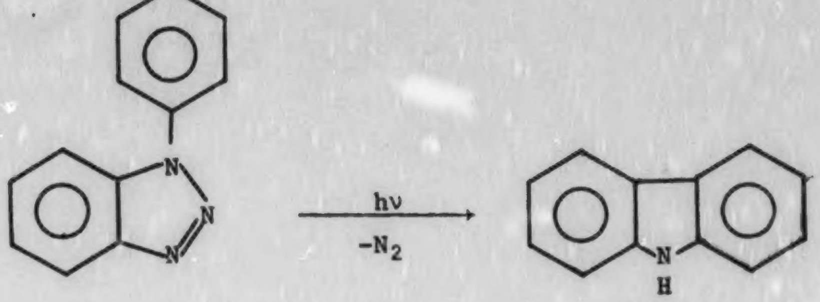
Because of their resistance to oxidation under environmental conditions, benzotriazoles placed in the environment, by whatever means, are likely to persist for long periods of time.

4. Photochemistry

Considering that benzotriazoles generally exhibit broad ultraviolet absorption (see Section I-A-3), the compounds which are the main concern of this work are, on the whole, remarkably stable to ultraviolet radiation, particularly at wavelengths encountered at the surface of the earth (300-400 nm). Nevertheless, benzotriazole and especially 1- and 2-substituted derivatives have been shown to rearrange and decompose if irradiated under certain laboratory conditions. These reactions and a theoretical explanation for the photochemical stability of the 2-(2'-hydroxyphenyl)-benzotriazoles are discussed below.

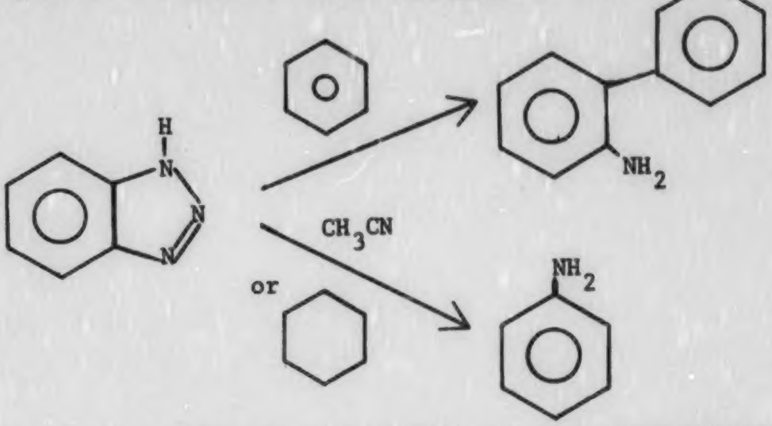
Irradiation in methanol at 300 nm transforms benzotriazole and certain of its 1-substituted derivatives into aniline and aniline derivatives, due to loss of nitrogen from the triazole ring and reaction with the solvent (Boyer and Selvarajan, 1969):



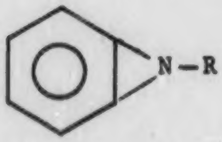


(carbazole)

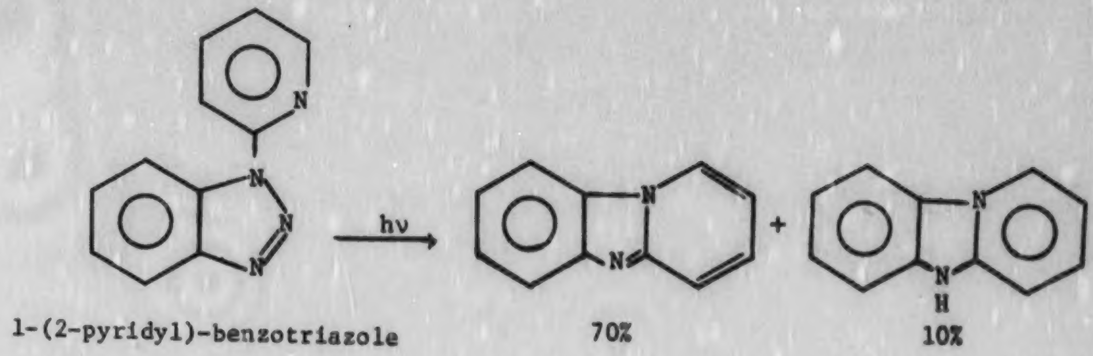
The low yield *o*-anisidine product results from using methanol as the solvent. In benzene, the sole product is phenylaniline; in acetonitrile or cyclohexane, the sole product is aniline (Tsujimoto *et al.*, 1972):

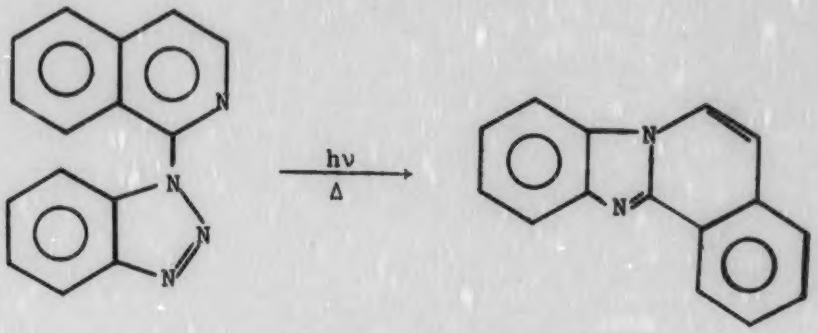


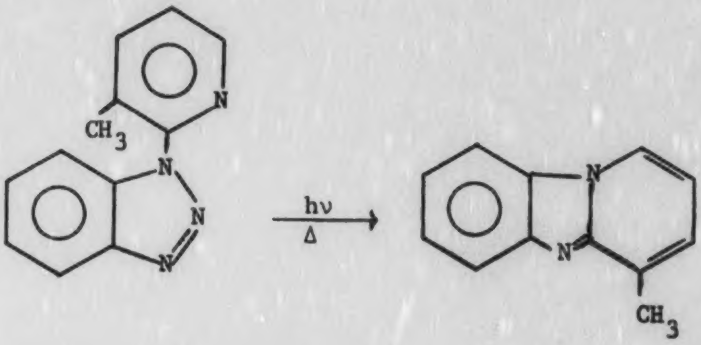
Either an electron delocalized intermediate or a benzoazirine,



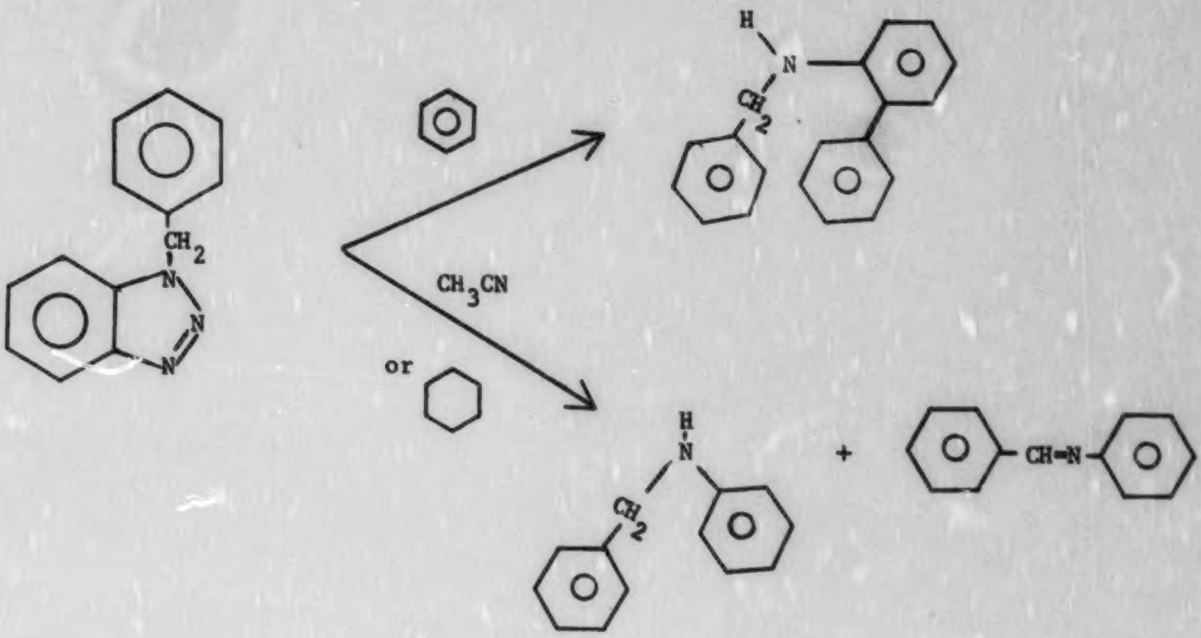
is believed to be the intermediate for these reactions. Similarly, benzotriazoles with 1-pyridyl and similar substituents produce mainly carbazole-like products on irradiation in ethanol with a high pressure mercury arc lamp (Hubert, 1969):



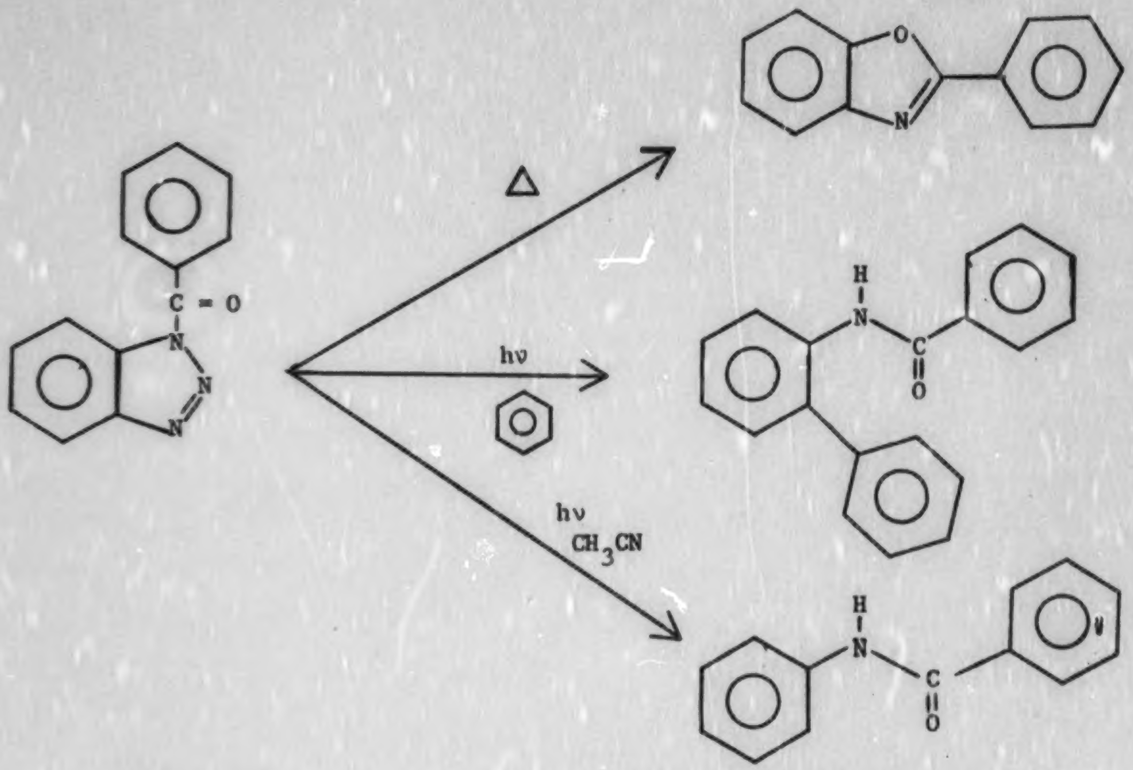




After four hours exposure to a 200 watt high pressure mercury arc lamp surrounded by a quartz filter (allows passage of 254 nm light), 1-benzylbenzotriazole produces the following products in solvent-dependent reactions (Tsujimoto et al., 1972):



These products are quite different from the main product of thermal decomposition of 1-benzylbenzotriazole, which is phenanthridine. Like 1-benzylbenzotriazole, 1-benzoylbenzotriazole also gives quite different products under conditions of thermal and photolytic degradation (Tsujimoto *et al.*, 1972):



A summary of the products formed during the photolytic decomposition of 1-benzylbenzotriazole at 300 nm in various solvents (Servé and Rosenberg, 1973) is listed in Table 9, which also lists the decomposition products of photolysis of 1-hydroxybenzotriazole and 1-methoxybenzotriazole at 300 nm in various solvents (Servé, 1974 a, 1974 b).

From the foregoing examples, it can be seen that the photolysis of 1-substituted benzotriazoles leads to the expulsion of nitrogen. This is accompanied by the generation of diradicals which are stabilized through intromolecular chemical reactions or reaction with the solvent (Servé and Rosenberg, 1973). In spite of the amount of attention these compounds have received in photochemical studies, it appears that 1-substituted benzotriazoles are not particularly important commercial materials.

Table 9. Photolysis Products of 1-Substituted Benzotriazoles at 300 nm in Various Solvents, % Yields (Servé and Rosenberg, 1973; Servé, 1974 a, 1974 b)

Product	In Benzene	In Methanol	In Acetonitrile	In Cyclohexane	In Water	In Dioxane
			1-Benzylbenzotriazole			
Phenanthridine	2	1	1			
Benzylidineaniline	1	42	69			
Bibenzyl	4	3	10			
Benzotriazole	2	3	2			
N-Benzyl-2-aminophenyl	80					
Aniline		15	8			
Benzylaniline		5				
o-Anisidine		13				
N-Benzylaniline		5	2			
o-Methoxy-N-benzylaniline		2				
			1-Methoxybenzotriazole			
1-Methylbenzotriazole	13	9	6	15		
Aniline		4	8	4		
Benzotriazole		9		28		
Azobenzene	63	61	81	11		
2-Aminobiphenyl	8					
Biphenyl	6					
Bicyclohexyl				8		
N-Cyclohexylaniline				24		
			1-Hydroxybenzotriazole			
Nitrosobenzene					67	45
Azobenzene					6	11
Diphenylamine					6	10
2-Hydroxyazobenzene					4	13
Azoxybenzene					8	18

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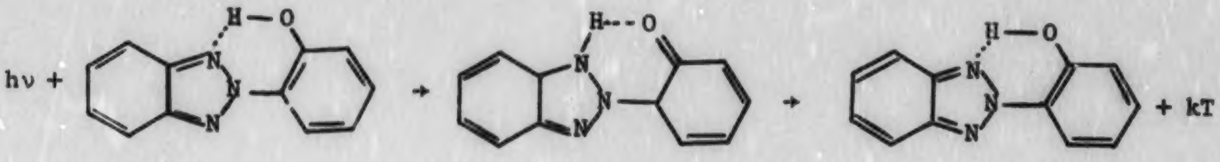
The 2-(2'-hydroxyphenyl)-benzotriazoles, with intramolecular hydrogen bonds, have low quantum yields in photochemical reactions (Otterstedt, 1973). The hydrogen bond can induce rearrangement of the molecular structure in the first excited state. The rearrangement, from enol to keto tautomeric forms, facilitates return to the ground state, thus providing a high degree of photostability for these compounds. The following equation illustrates the conversion of light into heat via an enol-keto-enol rearrangement (Tozzi, 1974):

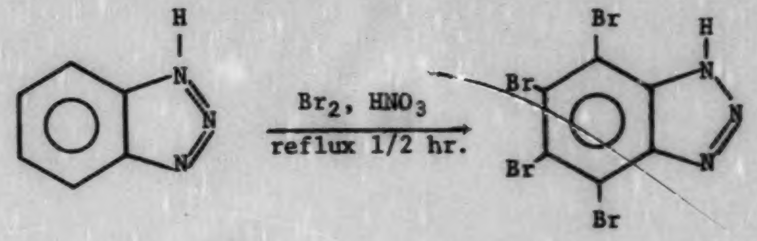


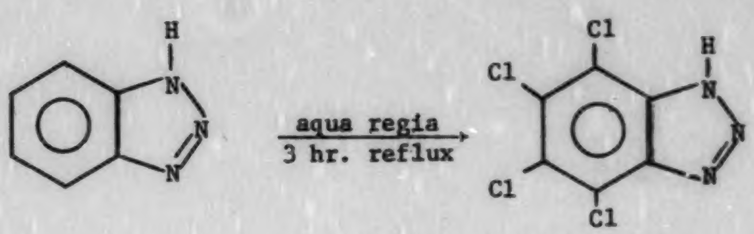
Self-consistent-field linear-combination-of-atomic-orbitals molecular orbital calculations (Otterstedt, 1973) indicate that the energy difference between the first excited state and the ground state is smaller in the keto form than in the enol form. Thus, conversion to the keto form in the first excited state provides a pathway for rapid nondestructive reversion to the ground state, and accounts for the photochemical stability of the Tinuvin compounds.

5. Other Chemistry

Some reactions which are of interest because of their potential environmental and/or toxicological impact include halogenation, nitration, and hetero-ring cleavage and rearrangement.

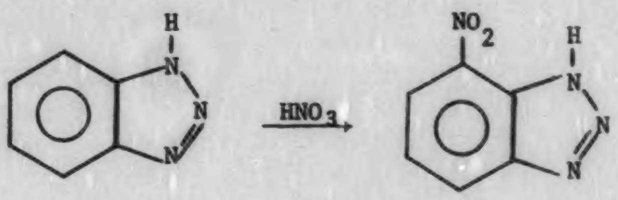
Both chlorination and bromination of the benzene ring will take place under the following strongly acidic, high temperature conditions:



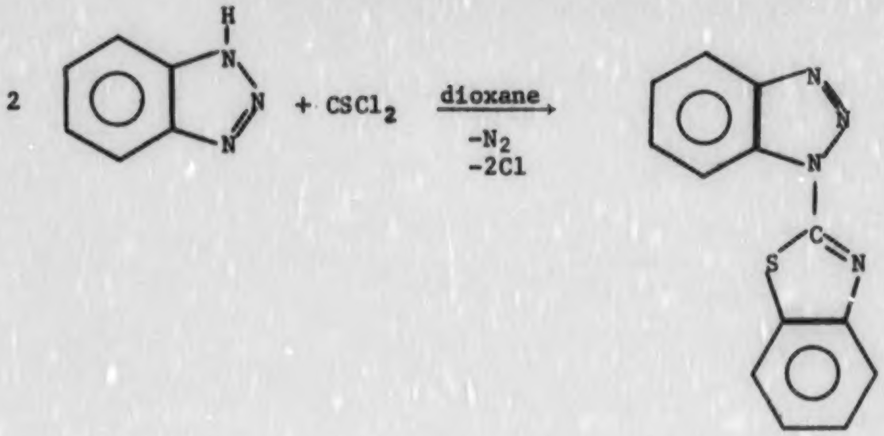


Because of the strenuous conditions required to completely halogenate the benzene ring, it is not likely these reactions will take place, for example, in a water processing or purifying plant where benzotriazole is present in the water either from external sources or from the use of anticorrosives on the machinery in the plant. Monohalogenation possibly occurs under somewhat milder conditions. Halogenation of the benzene ring increases the acidity of the hydrogen on the #1 nitrogen atom (see Table 8).

Nitration is achieved by reacting benzotriazole with nitric acid:



A rare and interesting cleavage and rearrangement of the triazole ring occurs when benzotriazole is reacted with thionyl chloride. The product is 1-(2-benzothiazolyl)-benzotriazole:



II. Environmental Exposure Factors

A. Production, Consumption

1. Quantity Produced

There are currently only five manufacturers of benzotriazole compounds in the U.S.A. Three of these produce benzotriazole itself. The remainder of the benzotriazole product line of each producer is unique. It would be relatively easy to trace production figures on the latter compounds to specific companies, were such figures available. Consequently, it is not surprising that production figures are not to be found in the literature examined, and the major companies involved are reluctant to discuss them. Nevertheless, based on information supplied in part by manufacturers and in accordance with the applications of these products, broad general statements can be made about production quantities of these materials. Even if vague, such statements are useful because they allow a better assessment of the potential environmental effects of these materials than would be possible without any figures at all.

The total production of benzotriazoles in this country probably ranges from about 4-10 million pounds per year, with 5-6 million pounds a most likely figure. The majority of this production is for the anticorrosion market. The Tinuvins account for perhaps 20-30% of production. Photographic uses consume roughly 200,000 pounds per year. 1-Chlorobenzotriazole is manufactured principally for use as a reagent chemical (it is an oxidizing agent) and is produced in quantities of about half a dozen pounds annually.

2. Producers

Table 10 lists the producers and production sites of benzotriazoles of commercial interest. Table 11 shows import data for Tinuvin compounds

Table 10. Producers and Production Sites of Benzotriazoles

Producer	Chemicals
Sherwin-Williams Chemical Company 501 Murray Road St. Bernard, Ohio 45217	1*H*-benzotriazole* monomethylbenzotriazoles (isomeric mixtures)* sodium tolyltriazole (aqueous solution of methyl benzotriazole isomers)
Fairmount Chemical Company 117 Blanchard Street Newark, New Jersey 07105	1*H*-benzotriazole 5-chloro-1*H*-benzotriazole 5-methyl-1*H*-benzotriazole
Eastman Kodak Company 343 State Street Rochester, New York 14650	1*H*-benzotriazole 5-methyl-1*H*-benzotriazole silver benzotriazole
Parish Chemical Company 815 West Columbia Lane Provo, Utah 84601	1-chlorobenzotriazole
Ciba-Geigy Corporation Polymer Additives Department Ardsley, New York 10502	2-(2'-hydroxy-5'-methylphenyl)-benzotriazole (Tinuvin P) 2-(3',5'-di-*t*-butyl-2'-hydroxyphenyl)-benzotriazole (Tinuvin 320) 2-(3'-*t*-butyl-2'-hydroxy-5'-methylphenyl)-benzotriazole (Tinuvin 326) 2-(3',5'-di-*t*-butyl-2'-hydroxyphenyl)-5-chlorobenzotriazole (Tinuvin 327) 2-(3',5'-di-*t*-pentyl-2'-hydroxyphenyl)-benzotriazole (Tinuvin 328)

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*35-50% isopropanol solutions of these chemicals are also produced.

Table 11. Imports of Tinuvin Compounds (pounds) (U.S. International Trade Commission)

Tinuvin	1970	1971	1972	1973	1974
320	2,315	2,646	2,204	6,613	22,047
326	9,701	24,476			
327			22,046	55,115	
327, MB-30, PS					90,058
120					3,306
P					23,777

over the last five years for which data is available. The general trend shown in the table is towards importing increasing amounts of these compounds.

3. Production Methods and Processes

Benzotriazole may be prepared on an industrial scale with yields up to 95% of theory according to the method of Levy (1966) by dissolving a quantity of 1,2-diaminobenzene (o-phenylenediamine) in water, acidifying with acetic acid (HAc), heating to 50-100°C and, while at this temperature, adding a sodium nitrite solution over a period of 0.5-2.0 hours, then continuing heating for a further period of time. The salt reacts with the acid to form nitrous acid which in turn reacts with the 1,2-diaminobenzene to form o-aminophenyldiazonium acetate which cyclizes to benzotriazole (see Section I-A-5). All reagents are added in stoichiometric quantities. The product may be extracted with a water-insoluble alcohol (butanols, heptanols, hexanols, etc.) and the extracted product recovered by solvent evaporation under reduced pressure. The product at this point is of relatively high purity, but may be further purified, if necessary, by recrystallization from a different solvent, such as benzene.

The main drawback to the above process is the solvent extraction step, without which the product is crude and must be cleaned up considerably, especially for photographic applications. The production of a high purity product without the need for the solvent extraction step (an expensive and time-consuming process on the industrial scale) is achieved by the method of Long (1971) (see Figure 6) wherein the pH of the reaction mixture is carefully controlled, initially to between 1.0-5.3 and after completion of the diazotization to 5.0-6.0. The benzotriazole oil which forms is separated from the

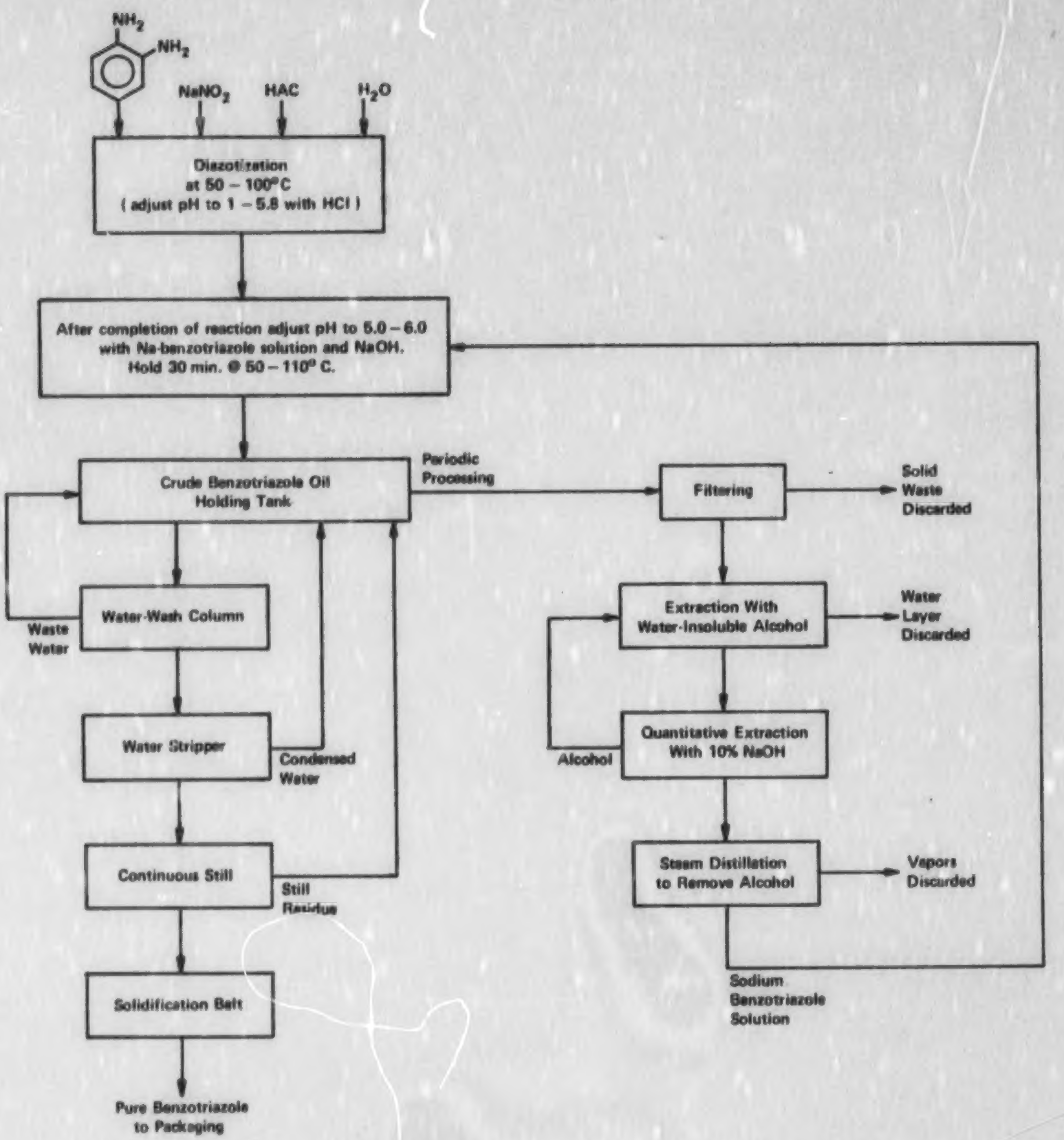

NH_2
NH_2
$NaNO_2$
HAC
H_2O
Diazotization at 50 – 100°C (adjust pH to 1 – 5.8 with HCl)
After completion of reaction adjust pH to 5.0 – 6.0 with Na-benzotriazole solution and NaOH. Hold 30 min. @ 50 – 110° C.
Crude Benzotriazole Oil Holding Tank
Periodic Processing
Filtering
Solid Waste Discarded
Water-Wash Column
Waste Water
Extraction With Water-Insoluble Alcohol
Water Layer Discarded
Water Stripper
Condensed Water
Quantitative Extraction With 10% NaOH
Alcohol
Continuous Still
Still Residue
Steam Distillation to Remove Alcohol
Vapors Discarded
Sodium Benzotriazole Solution
Solidification Belt
Pure Benzotriazole to Packaging

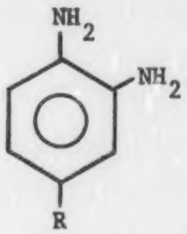
Figure 6. Commercial Preparation of Benzotriazole According to the Method of Long (1971)

reaction mixture and placed in a holding tank from which it is pumped through a column where it is washed with water. (The wash water goes back into the crude oil holding tank to prevent loss of the benzotriazole dissolved in it.) The washed oil is then stripped of water at 125-150°C and 80-100 torr. (The distillate is condensed and also returned to the holding tank to avoid loss of benzotriazole with the water.) The dry oil is then fed into a continuous still at 155-175°C and 3-5 torr. (The still residue is returned to the holding tank.) The distilled benzotriazole is condensed onto a stainless steel belt in a thin film. The solidified sheet is ground and packaged. Meanwhile, the remaining material in the holding tank is periodically processed prior to combination with the next batch of crude benzotriazole oil from the diazotization step. The processing involves filtering, discarding the solid waste, extraction of the benzotriazole with 2-ethylhexanol or similar water-insoluble alcohol (the aqueous layer is discarded), and quantitative extraction of the benzotriazole from the alcohol into a stoichiometric quantity + 10% of a 10% aqueous NaOH solution. The sodium salt which forms is soluble in water, but insoluble in the alcohol. The alcohol is removed by physical separation, then sufficient steam distillation is used to remove the remaining alcohol. The aqueous sodium benzotriazole solution is added to the reaction mixture containing crude benzotriazole. The overall yield of the process is 97% and the purity, measured colorimetrically, easily exceeds "photograde" specifications. Figure 6 outlines the steps of this process, which clearly are adaptable to the economics of a large scale, continuous, industrial process. It should also be obvious that the process is adaptable to the manufacture of various derivatives of benzotriazole. For example, starting with 1,2-diamino-3-methylbenzene instead of 1,2-diaminobenzene would yield a product mixture of 4- and 7-methylbenzotriazole.

The method of Long described above is likely the major industrial manufacturing method currently in use in the U.S.A. because a patent on it is held by the major producer of benzotriazoles, Sherwin-Williams Chemical Company. There are, however, other techniques described in both the patent and chemical literature for preparing benzotriazoles which may possibly be in use, especially in smaller scale operations. These, and a scheme for production of Tinuvin-type benzotriazoles, are discussed below.

Prior to the availability of the Long (1971) method for producing benzotriazoles, various procedures were in use to purify the crude diazotization product. These may still be used where access to the Sherwin-Williams technology is not available. One such method employs activated charcoal to remove colored impurities from the benzotriazole (Miller and Schlaudecker, 1958; Geigy Co. Ltd., 1965). Prior to charcoal filtration, the crude benzotriazole is dissolved in ethylene glycol or polyethylene glycol (McTeer and Kelso, 1972).

5-Substituted benzotriazoles can be prepared via diazotization from starting materials such as:



and reduction of the intermediate with a Raney nickel catalyst (J.R. Geigy A.G., 1965). A variety of R groups can thus be introduced to the benzotriazole molecular structure at the 5 position. If R is $-NO_2$, it can be reduced in the presence of a metal hydrogen catalyst to $-NH_2$. Acylation of $-NH_2$ in turn can yield an amide substituent. An $-NH_2$ can be replaced with a chlorine atom by heating in 1:1 HCl with CuCl (Arient and Dvorak, 1956).

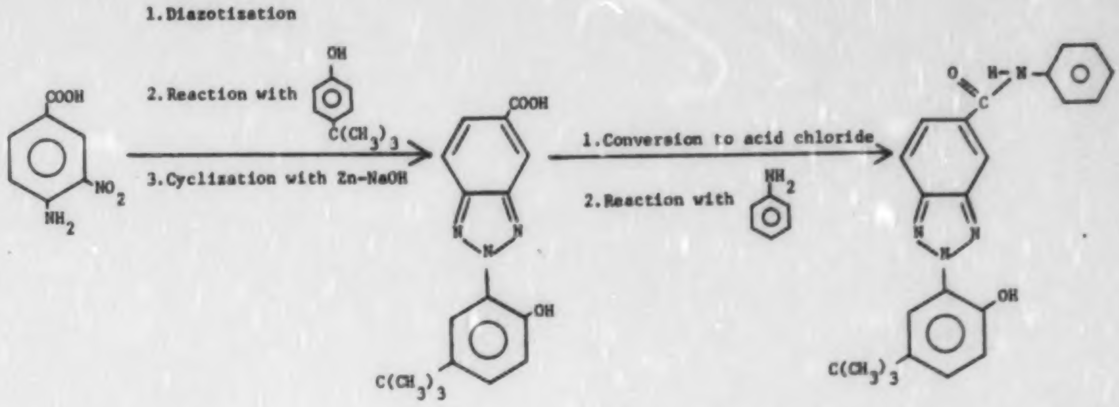
Benzotriazoles substituted at the 6 position have been prepared by the reduction of 1-hydroxybenzotriazoles with PX_3, where X is a halogen, alkoxy, or phenoxy group (Randell and Hargreaves, 1970 a, b). 6-Substituted benzotriazoles have thereby been prepared where R is methyl, methoxy, and chloro.

Triazinones have been converted into benzotriazoles in high yield (Rees and Sale, 1971), but like the 1-hydroxy synthetic route above, this is not a viable commercial method.

1-Aminoalkyl benzotriazoles have been prepared from benzotriazole and dialkylaminoalkyl chlorides in basic solution (Sparatore and Pagani, 1962). These are not of commercial interest, although they are of theoretical importance because the products are invariably mixtures of 1- and 2-substituted isomers, and the structure of the latter molecular type is still a matter of some debate (see Section I-A-1).

A wide variety of benzotriazoles have been prepared by the reaction of various organic azides with benzyne (Reynolds, 1964). 1-Substituted benzotriazoles, especially aliphatic substitutions, have recently been of interest because of their reported anti-inflammatory activity in rats (Kreutzberger and Van der Goot, 1974). The only 1-substituted benzotriazole that is commercially significant (in terms of monetary value of product manufactured) is 1-chlorobenzotriazole. This material is produced by the reaction of benzotriazole and NaOCl (see Section I-B-5). The reaction is rapid and quantitative; it probably proceeds by a free radical mechanism (Rees and Storr, 1969).

Compounds of the Tinuvin type [2-(2'-hydroxyphenyl)-benzotriazoles] may be prepared by coupling, under basic conditions and at room temperature, an _o_-nitrobenzenediazonium chloride with an appropriate phenol (Boyle and Milionis, 1965). A recent German patent (Herlinger and Kuester, 1975) describes the preparation of Tinuvin type compounds via the following reaction scheme:



4. Market Prices

Benzotriazole costs about \$2.75/lb. in 100-pound lots of technical material suitable for anticorrosion purposes. Photograde material is a good deal more expensive at approximately \$6-10/lb. on the same basis. Photograde derivatives of benzotriazole are priced considerably higher, especially in small quantities. 1-Chlorobenzotriazole, for example, sells for \$30/100 grams or about \$150/lb. (see also Anon., 1975; Anon., 1976).

Prices for Tinuvins are slightly higher than for other benzotriazoles made on a large scale, but price comparisons are not particularly meaningful since Tinuvins and other benzotriazoles are not competitive with each other.

Complete price listings are given in Table 12.

Table 12. Prices of Benzotriazole Compounds

Chemical	Basis	Price (lb.)	Effective Date	Manufacturer
Benzotriazole (technical) (Cobratec 99)	200 lbs.	2.80	2/76	[1]Sherwin-Williams
Benzotriazole (50% in isopropanol) (Cobratec 50-I)	400 lbs.	1.60	2/76	[1]Sherwin-Williams
Benzotriazole (technical)	100 lbs.	∿3	1/76	[2]Fairmount
Benzotriazole (practical)	500 gms.	51.04	1/76	[3]Eastman Kodak
Benzotriazole (photograde)	100 lbs.	5.50	2/76	[1]Sherwin-Williams
Benzotriazole (photograde)	100 lbs.	∿7	1/76	[2]Fairmount
Benzotriazole (photograde)	1 lb.	26.00	1/76	*Eastman Kodak
Tolyltriazole (technical) (Cobratec TT-100)	200 lbs.	1.93	2/76	[1]Sherwin-Williams
Tolyltriazole (35% in isopropanol) (Cobratec TT-35-I)	400 lbs.	.95	2/76	[1]Sherwin-Williams
Tolyltriazole, sodium salt (50% aq.) (Cobratec TT-50-S)	500 lbs.	.97	2/76	[1]Sherwin-Williams
5-Methylbenzotriazole (photograde)	1 lb.	55.55	1/76	[4]Eastman Kodak
Silver benzotriazole (photograde)	5 gms.	3300.00	1/76	[3]Eastman Kodak
Tinuvin P†	100 lbs.¶	6.35	8/74	[5]Ciba-Geigy
Tinuvin 320†	100 lbs.¶	6.35	8/74	[5]Ciba-Geigy
Tinuvin 326†	100 lbs.¶	8.50	8/74	[5]Ciba-Geigy
Tinuvin 327†	100 lbs.¶	6.75	8/74	[5]Ciba-Geigy
Tinuvin 328†	100 lbs.¶	6.95	8/74	[5]Ciba-Geigy

*Available in smaller quantities at higher per pound prices - see Anon., 1975.

¶For quantities 25-100 lbs., prices are about 5% higher; for less than 25 lbs., about 10% higher.

†See Table 10 for chemical names of the Tinuvins.

Sources: 1. Sherwin-Williams Co., 1975; Anon., 1976 b
2. Personal Communication
3. Anon., 1976
4. Anon., 1975
5. Ciba-Geigy Corp., 1974

Sherwin-Williams Company announced a 10% price increase effective February 2, 1976 (Anon., 1976 b), which is reflected in Table 11. Prices for small quantities from Eastman Kodak have decreased significantly (approximately halved) over the period 1974-1976 (Anon., 1974; Anon., 1976). The Kodak products, however, represent a very small part of the total benzotriazole market.

5. Market Trends

The trend appears to be towards increased production, especially in the dominant application, anticorrosion. Sherwin-Williams is doubling its capacity to produce benzotriazole and tolytriazole over the period 1976-1978 (Anon., 1976 a), which indicates the company's confidence in this market. If there is growth in the production of plastics which require the use of UV absorbers (polyolefins, for example), and photographic films, coupled with continued use of benzotriazoles in these products at present concentrations, total production of benzotriazoles could grow as high as 15-20 million pounds per year in the 1980's.

B. Uses

1. Major Uses

The major commercial applications of benzotriazoles are, in estimated order of quantity used: as an anticorrosion agent (particularly for copper and copper alloys); as an ultraviolet light stabilizer for plastics (especially polyolefins); and as an antifoggant in photography. Each of these major use categories is considered in turn below. Although photographic applications may consume a relatively small share of benzotriazoles, they are grouped with major uses because: 1) they represent a steady, well-established, and growing market for these chemicals; 2) there is an extensive literature (both chemical and photographic) on these applications; and 3) the quantity of benzotriazoles consumed in photography is probably much larger than all of the minor uses in Table 15 (p. 82) put together.

a. Anticorrosion Applications

The theoretical work of Dugdale and Cotton (1963), Cotton and Scholes (1967), and others (see Section I-B-1) on the mechanism of corrosion inhibition of benzotriazoles was preceded by many years of practical experience with benzotriazoles in anticorrosion applications. By the late 1950's the principal anticorrosion applications of benzotriazoles had been well-established. Benzotriazole was included in glycol-based antifreeze formulations in concentrations of 0.01-2.0% (Meighen, 1957), used for inhibiting corrosion of water pipe systems made of iron, copper, or their alloys in concentrations of 0.05% (Liddell and Birdeye, 1958), and also for inhibiting corrosion in hot water boilers in concentrations of 0.01-0.20% (Krietsch, 1958). In all of these applications, benzotriazole is used with other inhibitors. In the last case, for example, 1-2% triethanolamine phosphate is also present. Combinations of benzotriazole with nitrites and borates have been recommended (Liddell, 1959). In such formulations benzotriazole was found to be a more effective inhibitor than equivalent concentrations of thiocyanate ion or 2-mercaptobenzothiazole (Kendall _et_ _al_., 1959).

Antifreeze applications have been the subject of a number of patents, a typical example of which is illustrated by the recipe given in Table 13 for a glycol-based antifreeze which provides good protection for the metals customarily found in cooling systems, with outstanding protection for brass (Weichert and Hegemann, 1965).

Table 13. Typical Glycol-Based Antifreeze Anticorrosion Components (Weicher and Hegemann, 1965)

Inhibitor	Content, %, based on glycol
Sodium benzoate	1.50 - 3.00
Sodium benzotriazole	1.50 - 3.00
Borax	0.50 - 1.50
Sodium nitrite	0.50 - 1.50
Sodium carbonate	0.10 - 0.20
Benzotriazole	0.05 - 0.15
Sodium metasilicate	0.02 - 0.10
N-Methylmorpholine	0.01 - 0.10

Benzotriazoles can often replace sodium 2-mercaptobenzothiazole (NaMBT) on a cost-performance basis in glycol-type antifreezes. In one case 0.05-0.15% by weight benzotriazole was shown to give equivalent protection to 0.25% NaMBT when all other variables were held constant (Anon., undated). Not only does benzotriazole provide similar protection for copper, brass, bronze, cast iron, and steel components of automobile radiators, but it also provides superior thermal stability, chemical stability, stability to ultraviolet radiation, resistance to oxidation, a protective film which increases its protection with time, and lower toxicity than NaMBT (Anon., undated). The following examples illustrate some of these comparisons. In the presence of antialgal and antislime coolant additives, such as Chloramine-T, benzotriazole is stable, but NaMBT is destroyed by the released chlorine (Hatch, 1960; Albright and Wilson, 1961). At an operating temperature of

113°C for 1000 hours, the NaMBT content of an antifreeze was reduced by 88.5%, whereas under the same conditions the benzotriazole concentration was reduced by only 13.9% (Korpics, 1974 a). This data is shown graphically in Figure 7. The mechanism by which benzotriazole and sodium 2-mercaptobenzothiazole function as anticorrosion agents is fundamentally different. Benzotriazole forms a polymeric film (i.e., chemical bonds) on the surface of the metal, one or more layers of which shield the underlying metal molecules from further chemical attack. Sodium 2-mercapto-benzothiazole forms insoluble complex salts which coat the metal surface, protecting it from further oxidation (Santodonato et al., 1976), but which can be removed or disturbed by physical and chemical means more easily than the polymer coating formed with benzotriazole.

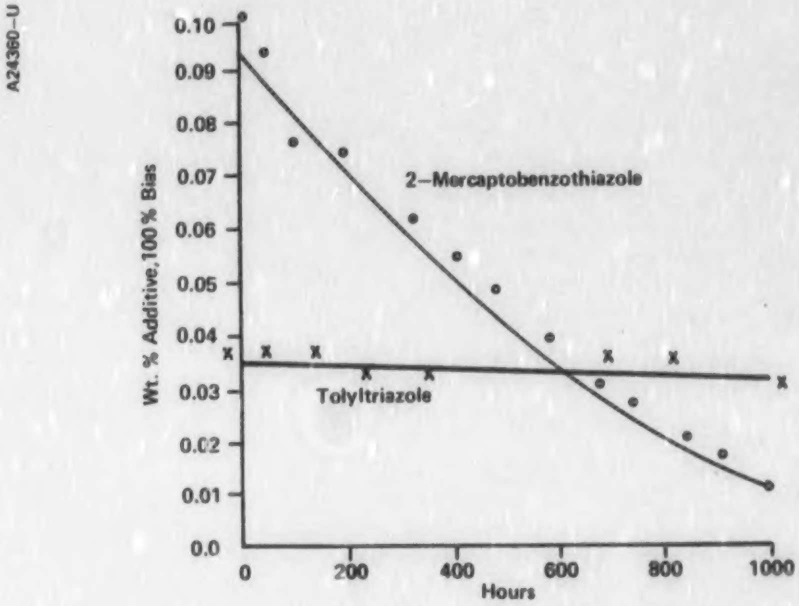
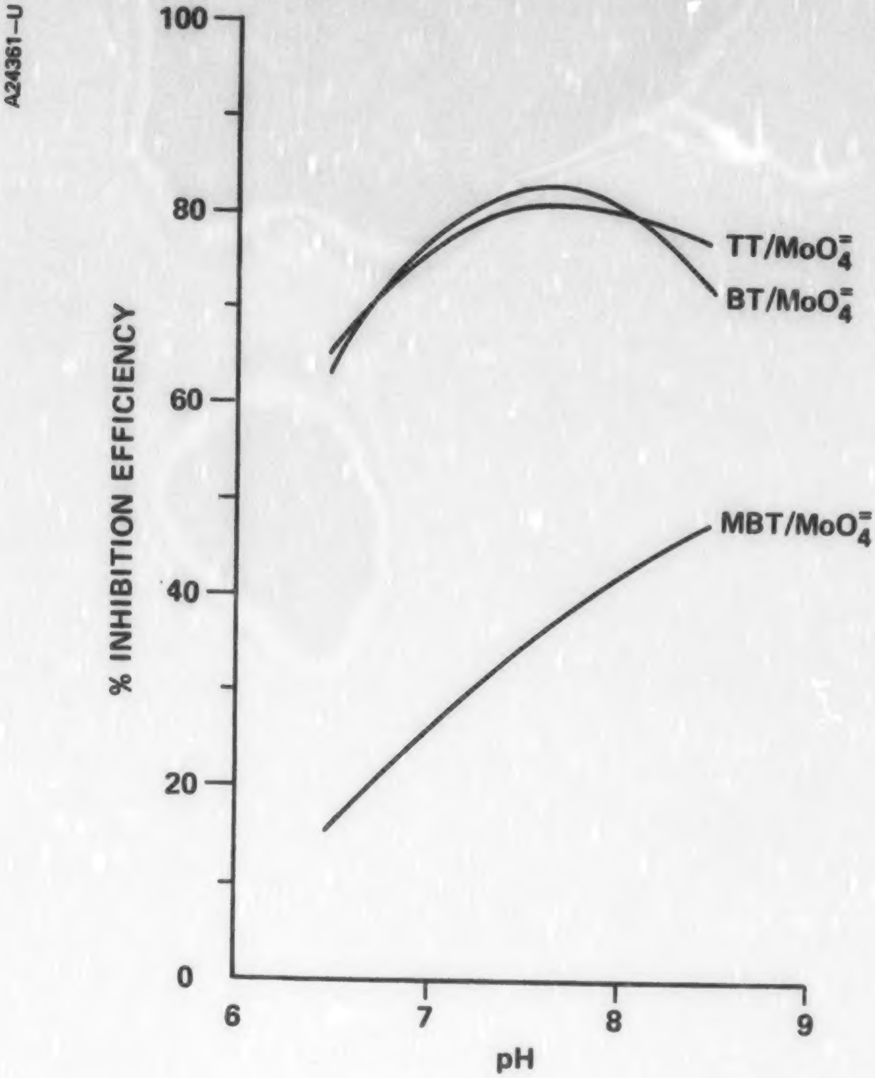


Figure 7. Automotive Antifreeze Thermal Stability Test-Depletion of Additive (Korpics, 1974 a)

The stability of the metal-benzotriazole polymer coating (particularly when the metal is copper) allows successful treatment for continuous protection of transient (as opposed to recirculating) water systems, such as domestic copper water lines. Surfaces to be exposed to water are degreased, washed with acid, then exposed to an isopropanol or water solution of benzotriazole or benzotriazole vapors. Copper-containing specimens contacted for two minutes at 60-100°C with 2% aqueous benzotriazole and dried at 60-90°C in the same vapor showed no pitting after three months in water that caused severe pitting in untreated specimens (Cotton, 1963), in a demonstration of the continuity of protection provided by benzotriazole.

Besides copper, benzotriazole is effective in protecting steel and other metals against corrosion in acidic aqueous environments (Sathianandhan et al., 1970). Derivatives of benzotriazole are effective as well. For example, 1-hydroxybenzotriazoles have been used to inhibit corrosion in boilers, coolers, and storage tanks (Tanaka and Tanigawa, 1974). Aluminum and mild steel, as well as brass and copper, were protected in a closed water system simulating a cooling tower by benzotriazole and triethanolamine mixtures (Chemed Corp., 1975).

A combination of molybdates and benzotriazoles has inhibited corrosion of brass/steel systems more effectively than the single active components used alone, and was significantly superior to 2-mercaptobenzothiazole, especially at higher pH's (see Figure 8) (O'Neal and Borger, 1975). Similar results are claimed in a study commissioned by the Sherwin-Williams Chemical Company (Sherwin-Williams, undated a) in which the superiority of benzotriazole over 2-mercaptobenzothiazole is demonstrated in a nitrite-borax inhibitor system



TT/$MoO_4^=$	tolyltriazole + molybdate
BT/$MoO_4^=$	1$\underline{H}$ – benzotriazole + molybdate
MBT/$MoO_4^=$	2 – mercaptobenzothiazole + molybdate

$$\%\ \text{Inhibition Efficiency} = 100 \times \left(1 - \frac{\text{weight loss inhibited sample}}{\text{weight loss control}}\right)$$

Figure 8. Effect of pH on Percent Inhibition Efficiency for Steel in Simulated Cooling Water (O'Neal and Borger, 1975)

at pH 8.5. At pH 8, benzotriazoles teamed with lhydroxyethylidene-1,1-diphosphoric acid (HEDP, marketed by Monsanto Co. under the tradename Dequest) outperform triazolemolybdate combinations, especially with respect to the protection of steel (O'Neal and Borger, 1975).

An example of a specific application of benzotriazole for inhibition in a water-cooled stator in a power plant has been described by Wall and Davies (1965). One problem encountered with corrosion in such situations is that it leads to an increase in conductivity of the water, which increases the risk of energy losses and flashovers (sparks) since the stator and heat exchanger are approximately 7,000 volts apart in potential. It was concluded that the rate of increase of conductivity of the cooling water was reduced with the use of benzotriazole, thus increasing usage periods between system flushing. Also, 20-100 ppm of benzotriazole in the cooling water eliminated the need for a costly demineralizer system. In another study concerning the use of benzotriazole in a closed water cooling system, Hoyer _et al_. (1968) concluded that benzotriazole reduced corrosion in a high energy particle accelerator, the inhibiting effect manifesting itself as an apparent reduction in the available copper surface area.

Benzotriazole is incorporated into wax and polishing formulas designed for cleaning and protecting copper and other metals. Concentrations of 0.1-10% benzotriazole dissolved in the wax or polish or added in a solvent proved effective in protecting copper sheets exposed 24 hours to a 0.25% salt solution mist which badly stained unprotected samples (Cotton, 1964). Typical concentrations of benzotriazole in these formulations are 0.1-1.0% (Geigy A.G., 1965 a). Chromium plated steel can be protected by the same formulations (Cotton, 1965). It is likely tnat benzotriazole is in polishes and cleansers currently marketed for chrome plated automobile parts as well as body waxes.

Machined and fabricated parts of copper or copper alloys manufactured for later assembly are effectively protected against staining and corrosion in storage and transportation by enclosure in tissue paper, kraft paper, or paperboard containing 2% benzotriazole or tolyltriazole by weight (Korpics, 1974 b). This "vapor phase" protection is possible because of the appreciable vapor pressure of these benzotriazoles under ambient conditons. Tissue paper is impregnated by spraying with a 1% isopropanol solution. Paperboard is impregnated so that the final concentration is about 0.2 gram benzotriazole per square inch. At these concentrations effective protection can be expected for more than one year in an industrial environment.

The natural color of copper suggests many decorative architectural uses, particularly outdoors. In such applications the color can be maintained for at least several years by coating the copper with a transparent lacquer containing benzotriazole corrosion inhibitors. Incralac, a finish developed by the copper industry, is an example of such a lacquer which preserves copper and copper alloy architecture both outdoors and in (Anon., 1969). Incralac contains an acrylic ester resin dissolved in a solvent such as toluene, benzotriazole, and epoxidized soya bean oil as a leveling agent. A UV absorber (such as Tinuvin) and an antioxidant are also added to prevent breakdown of the lacquer under the influence of UV radiation. The final cleaning step prior to application of the lacquer consists of wiping the metal surface with a solution containing 40 grams benzotriazole per gallon of water. The 230,000 square foot geodesic dome copper roof of the Sport Palace in Mexico City erected for the 1968 Olympics is an example of an outdoor structure protected by Incralac (Anon., undated). One limitation of Incralac is that the coating is rather soft. Therefore, for handrails and other items subject to wear and/or physical abuse, coatings have been developed based on polyurethanes containing 1.5% benzotriazoles (Walker, 1970).

There are a number of other film-forming products which contain 0.05-1.0% benzotriazoles to prevent discoloration. These include bronze-pigmented paints, inks, and lacquers (Aiken et al., 1965; Keino and Nakato, 1972). In addition to protecting newly manufactured articles, benzotriazole is used to protect restored ancient bronze objects. After cleaning, vacuum impregnation and the use of lacquers are the chief methods of applying the inhibitor (Madsen, 1971; Marabelli and Guidobaldi, 1972).

Benzotriazoles are added to lubricants, greases, and dielectric oils to prevent them from attacking metals in contact with them. For example, organosiloxane greases useful as lubricants, dielectrics, and sealing compounds are made less corrosive to copper and steel by the addition of 0.02-0.06% benzotriazole (Midland Silicones Ltd., 1959). Greases thickened with organophilic bentonite are rust-inhibited by the addition of less than 0.5% by weight benzotriazole (Donaldson et al., 1965). Lubricating oils are protected against oxidation by the addition of benzotriazole (Malec, 1975). Hydraulic fluid consisting of a mixture of polyglycol ethers and vegetable oils is effectively prevented from chemical interaction with rubber and metal parts of hydraulic systems by the addition of ~0.25% benzotriazole (Stein, 1961). Sulfur containing insulating oils (dielectrics) are inhibited from attacking copper without influencing the efficiency of the electrical apparatus by the addition of 1-50 grams of benzotriazole per kiloliter of oil (Fugita, 1974). A copper sheet dipped into inhibited oil containing 0.22% sulfur reacted with

1.4 μg of sulfur when 30 kilovolts electromotive force was applied, whereas 13.9 μg of sulfur was consumed from uninhibited oil.

Finally, benzotriazoles are used in anticorrosion applications in both aqueous and nonaqueous cleaning systems. Dry cleaning solvents (such as chlorinated hydrocarbons and petroleum naphthas) and detergents (such as petroleum sulfonates, alkylamine sulfonates, aryl phosphates, and benzene sulfonates) cause corrosion of the metals in the cleaning machines, especially copper, which results in discoloration of the cleaning fluid and the possibility of staining light colored clothing. Corrosion can be prevented by the initial addition of 10-250 ppm benzotriazole or alkylbenzotriazole to the solvent-detergent system. As long as at least 10 ppm benzotriazole are maintained in the system, corrosion is prevented (Levy et al., 1967). Benzotriazole and alkylbenzotriazoles have also been recommended in the formulation of dishwater detergents (Ciba-Geigy, 1972 a). Approximately 0.05% benzotriazoles prevents the corrosion of copper and metal parts of the washing machine, and inhibits tarnishing of metal pots and silverware by other detergent ingredients.

b. Ultraviolet Stabilization Applications

A number of polymers, especially certain polyolefin plastics, some oils, and various paint pigments which are subject to degradation upon exposure to ultraviolet light are protected from the consequent undesirable physical changes which ensue by incorporation of ultraviolet stabilizers, such as benzotriazoles. Benzotriazole stabilizers absorb incident ultraviolet radiation and dissipate it harmlessly as heat. The discussion below includes specific examples of the kinds of materials which have been successfully stabilized against UV degradation by benzotriazoles. It is interesting to note that this application is not restricted to 2-(2'-hydroxyphenyl)-benzotriazoles (Tinuvin type).

Although the Tinuvins are better UV absorbers than most other benzotriazole derivatives, the simpler structures are often quite adequate for some applications.

One of the most widely used plastics stabilized with benzotriazoles is polypropylene. Tinuvin type compounds are usually used, generally in combination with other UV absorbers (Cantatore and Bordini, 1963; Compostella, 1964) and antioxidants (Balaban, 1964). Other plastics and polymeric materials which have been protected with benzotriazoles include polyesters (Yamaguchi et al., 1975), cellulose acetate, nylons, polyvinyl chloride, and polymethyl methacrylate (Heller et al., 1961). Plastics pigmented with titanium dioxide have improved ultraviolet stability when a 2-(2'-hydroxyphenyl)-benzotriazole is included in the formulation (Zannucci et al., 1975). Plastics intended to be light-degradable have been insured stability while still in service by means of a water soluble coating containing a Tinuvin type compound. Upon discarding the container, the coating is readily washed away, leaving the plastic subject to rapid degradation by light (Fischer, 1973). Such an external coating also has the advantage of avoiding the possibility of migration of the stabilizer into the original contents of the container. This is very important when such contents are food products. The Food and Drug Administration has set the maximum concentration of 2-(2'-hydroxyphenyl)-benzotriazoles at 0.25% in polystyrene and/or rubber modified polymers intended to contact nonalcoholic food (Anon., 1972).

Degradation of polypropylene is catalyzed by copper. Consequently, copper electrical wires with polypropylene insulation have presented a special problem, since unprotected wiring exposed to sunlight and copper degrades quite rapidly (Hansen et al., 1965). Benzotriazoles have been among the most successful stabilizers in retarding both the interaction of ultraviolet light with the polypropylene insulation and also the copper wire with the polypropylene (Hansen, 1968). Benzotriazoles thus used include the parent compound and the 5-chloro, 5-methyl, 5-nitro, and 5,6-dimethyl derivatives with and without antioxidants. In an application where copper sheets were laminated on both sides with polyethylene, the polymer was protected from catalytic degradation by incorporation of zinc benzotriazole and lead benzotriazole salts into the polymer matrix (Kuroha et al., 1975).

Besides clear polymer coatings, some paint and varnish coloring matter is also stabilized by benzotriazoles. For example, the discoloration of nitrophenol azo dyes in varnishes due to contact with iron in the presence of small amounts of water is prevented by including 0.005-0.2% by weight benzotriazole in the formulation (Werner and Langstroth, 1958). Treating a red pyrazolone pigment with a chlorobenzotriazole (probably 5-chlorobenzotriazole) stabilizes it when used as a polymer dye (Kriisa, 1970).

Benzotriazole has also been used to stabilize oils used as solvents for fungicides intended for tropical and semitropical crops, including citrus fruit, bananas, cacao, and coffee. Ultraviolet radiation catalyzes the oxidation of the solvent oils, resulting in the formation of acids and perioxides which are toxic to the plants and cause almost as severe a crop loss as the fungi the spray is supposed to control. The addition of benzotriazole to the oil (antioxidants can be substituted as well) protects the oil from oxidation and prevents crop losses from that source (Harrison, 1963). In other biocontrol applications, Tinuvin products have been used to stabilize an insecticide which inhibits larval development (Letchworth and Pallos, 1972), for photostabilization of insect moulting hormones (Ferrari et al., 1973), and for the protection of silk fibres from photodegradation (Kuwahara et al., 1974).

Tinuvin compounds have also been used in suntan lotions, ostensibly to reduce the level of ultraviolet light absorbed by the human skin (Heller et al., 1961).

c. Photographic Applications

Benzotriazoles are well-known antifoggants which are present in small quantities in the emulsions of many photographic products. They are effective for the same purpose in photographic developers, although they are not found in the standard formulas used for general amateur and professional photofinishing. Benzotriazoles are also used in a variety of other photographic applications including monobaths, heat sensitive copying, and dye diffusion processes (as typified by Polaroid Land products). Most of the information on these various uses is available in the patent literature, and it is therefore not possible to be certain that currently marketed processes conform exactly to these descriptions. However, the examples below were chosen because they appear to be relevant to presently available products.

The diversity of benzotriazole derivatives useful as antifoggants is exemplified by an Ilford Ltd. patent (Brown et al., 1971) which describes at least two dozen benzotriazoles which are useful as antifoggants for X-ray film at concentrations of 330 mg/g·mole silver halide in the emulsion. Image (optical) densities of fog value 0.04 are obtained with 4-nitro-5-methyl-1H-benzotriazole in the emulsion as compared to 0.35 fog density without the antifoggant. Also, the contrast range of the emulsion with the antifoggant is about 20% greater than the contrast range without the antifoggant. A General Aniline and Film Corp. patent (Popeck and Sottysiak, 1959) describes the use of 5-nitro-1H-benzotriazole in a paper emulsion. The benzotriazole is incorporated into the emulsion (250 mg/100 gm $AgNO_3$) and also into a protective gelatin overcoating (30 mg/kg gelatin), yielding a fog-free image resistant to fading or aging. Fuji Photo Film Co. (Ohkubo et al., 1971) reports that 5-bromo and 5-methylbenzotriazoles in paper emulsions in concentrations of approximately 10^{-5} - 10^{-3} mole/mole Ag^+, produce low fog, high density, high contrast images.

The presence of 1H-benzotriazole in paper emulsions tends to result in a "cold" image tone; the image is often described as "blue-black" rather than "neutral-black" (John and Field, 1963). Velox and Velox Premier papers manufactured by Eastman Kodak Company, widely used in large mass production commercial photofinishing operations, are examples of well-known blue-black emulsions which almost certainly contain benzotriazole. Tone differences between blue-black and neutral-black emulsions processed in the same developer are subtle; emulsion tone can be widely varied, however, by length of exposure, chemical composition of the developer, and the use of chemical toning processes. There is no indication that benzotriazole in developers or toners affects emulsion tone. However, when benzotriazole and 1-phenyl-5-mercaptotetrazole are incorporated into a cover layer (but not the emulsion layer), the resulting paper print image is resistant to changes in image tone produced by high gloss heating (drying) methods typical of mass photofinishing (Gaffin, 1970).

Antifoggants usually reduce effective film speed by their restraining action on the developer. However, the effect of benzotriazoles on film speed seems to be variable. Silver benzotriazole appears to reduce emulsion speed (Faerman and Pletnev, 1957), but 1-methylbenzotriazole is said to increase emulsion speed (Sturm and Kralove, 1961).

Benzotriazole is occasionally added to standard developer formulas when films or papers tend to show fog from excessive age, unfavorable storage conditions, or when long periods of time have elapsed between exposure and development (Anon., 1973). While this is a commonly cited use in black and white photography, it probably accounts for an insignificant quantity of the benzotriazole used in photography. The only regular employment of benzotriazole in processing solutions in the available literature is in monobath formulations such as Speers (1974). A monobath is a solution which develops and fixes film in one step. The developing agent must be of high activity and the silver ion solvent of relatively low activity. Although useful in certain extremely urgent applications or recording instrument data readouts, films processed in monobaths usually lack characteristics desirable in general photography, such as fine grain, high acutance, and good shadow detail.

Although less sensitive to light than silver halides, silver benzotriazole in combination with silver halides is adaptable to certain photocopying techniques. It is used in a heat-developable copy system in which the light sensitive material is developed, after exposure, by heating for 10 seconds at 160°C. Once developed, the copies are stable to further exposure to light (Ohkubo _et_ _al_., 1972). A similar material containing silver 5-chloro-1_H_-benzotriazole is light insensitive _until_ heating for 5 seconds at 180°C, then may be exposed as usual and developed by further heating for 5 seconds at 200°C to yield a brown positive image (Takekawa _et_ _al_., 1973). Benzotriazole has also been used in a non-silver thermographic duplicating process developed by Minnesota Mining and Manufacturing Co. (1966), but has not become as popular as the xerographic (electrostatic) processes of Xerox Corp. or IBM Corp. because it has not been able to compete in terms of clarity and stability of image, time, and cost.

Besides being used for document copying, benzotriazole can be used in processes for rendering documents and microfilms duplication-proof. Most microfilm copying systems use photosensitive materials that are mainly sensitive to light in the blue and ultraviolet range, but practically not at all to green or red. Therefore, the incorporation of an ultraviolet absorbing 2-(2'-hydroxyphenyl)-benzotriazole compound into the emulsion or base of a microfilm, for example, makes the film opaque to the light to which the copy material is most sensitive, making it difficult or impossible to achieve clear copies. At the same time, the benzotriazole-containing base transmits light visible to the human eye, and so the treated microfilm is as suitable for viewing or projection as untreated microfilm (Buckley and Goffee, 1973).

In an Eastman Kodak patent describing silver halide sensitive copper printing plates, 4-nitro-6-chloro-1H-benzotriazole is included in the emulsion recipe. The presence of benzotriazole in the developer is said to improve adhesion of the relief image (Abbott, 1969). The extent of the use of benzotriazoles in photographic printing plate processes is not known.

A final likely application of benzotriazoles to black and white photography is in stabilization processing in making prints. Stabilization processing employs special photographic paper which has developing agents incorporated into the emulsion during manufacture. The exposed paper is processed by inserting it into a machine. In the machine the emulsion of the paper is coated with a high pH "activator" solution which causes rapid uniform development of the image. The paper is then immersed in a low pH "stabilizer" solution, is squeegeed, and emerges from the machine practically dry, stable to light, and ready for immediate use. The whole process takes seconds compared to over an hour for processing, washing, and drying a conventional photographic paper. However, because all of the residual silver halide and processing chemicals have not been removed from the stabilized print, it eventually deteriorates. Stabilized prints may be made permanently stable by the usual fixing and washing procedures any time within several months of development (before fading and staining commence). Stabilization processing enjoys wide use wherever speed and convenience are critical such as police work, medicine, journalism, and professional studio proofing, especially when a permanent print is not necessary. It may eventually become a very significant factor in the home darkroom market since small processing machines costing as little as $150 are available. According to Eastman Kodak Company (Anon., 1973 a), which manufactures professional stabilization processing machines as well as paper and chemicals, stabilization activator solutions probably contain less than 0.01% antifoggant, stabilizer solutions between 0.1-1.0% antifoggant. The antifoggants, which are not specified, may or may not be benzotriazoles. Most stabilization processing formulas are considered proprietary. However, the use of UV absorbers in the stabilizer solution (as well as the emulsion and base of the paper) would seem to be a practical means of protecting a nonpermanent image from actinic light. If benzotriazoles are in the solutions, this would apparently be the only type of black and white processing solution which regularly contains them, aside from monobaths, and it is an area where growth in use is expected.

In color photography benzotriazoles are used both as antifoggants and ultraviolet stabilizers. In the antifoggant application benzotriazoles are apparently incorporated into color emulsions (Moll et al., 1973) (as in black and white photography) rather than developer solutions. The current

Eastman Kodak Ektachrome E-4 process for transparencies may employ an antifoggant in the prehardener solution (Anon., 1973 a), but E-4 will be replaced between late 1976 and early 1977 with a new process (E-6) which does not have a prehardener step (Anon., 1976 e). Processed color images consist of complex dyes which are subject to degradation upon continuous exposure to light, especially ultraviolet light. Benzotriazoles may therefore be present in color dye stabilizer solutions (Anon., 1973 a) (usually the last step in a color process), although protection is apparently more successful when the UV stabilizer is incorporated into the emulsion layers and support base during manufacturing (Crawford and Hartman, 1967).

Benzotriazole is used in direct-positive dye diffusion-transfer color processes. In an application suggested by Polaroid Corporation (Ciecluch and Schlein, 1973), Tinuvin 327 or 328 is placed in the polyester film support beneath the positive image receiving layer in concentrations of 50-75 mg/0.09 m^2. In an Eastman Kodak patent (Crough and Snyder, 1973), the negative emulsion contains three parts benzotriazole, presumably as an antifoggant. Benzotriazole may also be in the monobath (chemical packet whose contents coats the negative and receiving layers during processing) of dye diffusion processes, where its presence is said to have a great effect on the quality of the color image (Loznevoi _et al_., 1975). "Instant" color film, already a significant factor in the amateur market, is likely to become even more important since Kodak announced its dye diffusion process (Anon., 1976 c). Cameras and film will be marketed in the U.S. by the end of June, 1976, and Kodak is offering other camera manufacturers aid in designing cameras to use the new Kodak film (Anon., 1976 d).

A final application for benzotriazoles in color photography, and one which may have excellent growth potential, is the use of benzotriazole compounds in heat-developable color emulsions. Eastman Kodak Company has produced a color process employing silver benzotriazole, which develops by heat without any chemical solutions (Anon., 1975 b). Based on what is known of the use of silver benzotriazole in black and white thermal developing copiers, the most likely use for such a color process seems to be in a color copying and duplicating device.

The major uses of benzotriazoles are summarized in Table 14.

2. Minor Uses

Under the category of minor uses are applications of benzotriazoles in analytical chemistry, the petroleum industry, biology, and numerous other areas, examples of which are provided below. Obviously, the division between major and minor applications is somewhat arbitrary, since it cannot be done on a quantitative basis with any precision, there being little quantitative information on major uses and none at all on minor ones. One yardstick for categorizing a use as minor has been the amount of available literature on that use with the assumption that the most economically significant uses often get the most attention. Another has been the assessment of industrial sources on the relative importance of various uses to the total market. An attempt has been made to include under minor uses those applications which may not at present be of great economic significance, but may have some potential environmental impact either now or sometime in the future.

1-H-Benzotriazole is an important analytical reagent for noble metal determinations, especially copper and silver. It forms insoluble complexes

Table 14. Major Uses of Benzotriazole Compounds

ANTI-CORROSION -	antifreeze compositions
	hot water heaters and associated pipes of iron, copper, and their alloys
	electric generator water cooling systems
	cleaning pastes and polishes
	impregnated protective paper (for packing, wrapping, and storage)
	dry cleaning fluids
	dishwasher detergent
	metal lacquers
	hydraulic and lubrication fluids
	electrolytic deposition (improves hardness and brightness)
ULTRAVIOLET STABILIZATION -	plastics, especially polyolefins
	other polymers, such as nylons and polyesters
	clear coatings
	paints and pigments
	oils
PHOTOGRAPHY -	antifoggants
	emulsion tint agent
	UV absorber/stabilizer
	thermographic photocopying processes

with both these metals, which reactions are easily adapted to quantitative gravimetric assays (Akiyama and Terano, 1964). Potentiometric determinations of the following cations with benzotriazole at various pH values have been reported (Havir, 1967): Ag^{+}, Cu^{+}, Cu^{++}, Hg_2^{++}, Cd^{++}, Ni^{++}, Co^{++}, Mn^{++}, and Zn^{++}. In a typical assay, samples of silver ion (6-40 mg) were determined with a standard deviation of ±1.4% in the presence of 50-65 mg of Zn^{++} or Mn^{++}, which did not interfere. The amperometric determination of Cu^{++} with benzotriazole (Poddar and Ray, 1970) and Ni^{++} and Co^{++} (Poddar and Ray, 1973) in the presence of each other and also ions of calcium, magnesium, aluminum, iron, chromium, and lead, has also been reported. The lack of cross-interferences in these methods suggests their use in a number of applications, including mining and effluent analysis.

Other transition metals form stable complexes with benzotriazole. Palladium (II), for example, reacts readily to form a bis complex (Watanabe et al., 1972). The reaction is almost quantitative. An interesting aspect of this reaction is the tendency (shared by other metals) to form salts (rather than coordination complexes) by replacement of the #1 proton with a metal cation. This side reaction can be avoided by either running the reaction in highly acidic aqueous media (an environment unfavorable to the ionization of benzotriazole) or in an aprotic solvent, such as xylene (House and Lau, 1974).

Of the few spectrophotometric methods developed for the determination of halides, sulfate, sulfide, and like anions, one unique approach involves exchange spectrophotometry with silver benzotriazole, selected because of its greater solubility in the water/organic solvent medium chosen than silver salts of the anions to be determined. In effect, free benzotriazole replaces the anion of interest in the solution. The benzotriazole concentration, which is then equivalent to the concentration of the ion of interest, is measured spectrophotometrically (Kirsten, 1956).

Benzotriazoles have been involved as synthetic intermediates. A Japanese review (Munekata and Sahakibara, 1973) discusses the use of 1-hydroxybenzotriazole in peptide syntheses.

A number of uses for benzotriazoles have been reported in the petroleum industry. Small quantities of benzotriazole (or other nitrogen-containing heterocycles) raise the research octane number of gasoline when added to catalytic cracking feedstocks (Viland, 1958). Synthetic lubricating oils designed especially for gas-turbine engines are less likely to attack silver or copper-containing metals if 0.05-5.0% by weight benzotriazole, methyl benzotriazole, or other nitrogen heterocycles are included in their formulation (Elliot and Edwards, 1961). A lubricating emulsion useful in glassworking, and which may be safely disposed of in a conventional sewage system, contains 0.5% by weight benzotriazole (Zuraw, 1970). This biodegradable lubricant is said to have no adverse effects on an activated sludge sewage system. No data was given on the fate of the benzotriazole. Because the lubricant formula indicates 25% by weight natural winter sperm oil, it probably has been reformulated or abandoned on account of the ban on use or importation of whale products in this country. The patent (U.S. #3,507,792) is held by Sinclair Research, Incorporated.

An industrial application for benzotriazoles which could potentially consume large amounts of these chemicals has been described by Hirakawa and Sakai (1973). They suggest that plating steel tire cord with zinc or a zinc-copper alloy, followed by treatment with a benzotriazole prior to tire manufacture, results in a superior rubber-to-cord adhesion and reduced cord corrosion. There is no information in the available literature as to what extent, if any, benzotriazoles are being used for this purpose.

Biological applications of benzotriazoles have generally involved their use to synthesize other complex molecules, such as those containing sulfonyl (Sasse et al., 1961) or sulfenyl (Margot and Gysin, 1959) moities, which are properly outside the scope of this report. An example of these is 1-trichloromethanesulfenyl-4-nitro-5-chlorobenzotriazole. These compounds have been recommended for their antifungal activity when applied as dusts or aqueous emulsions on plants, wood, textiles, hides, and leather. Benzotriazoles have also been studied for their antiviral activity (Tamm et al., 1961) (see also Section III-B-5). Carboxamide derivatives of benzotriazoles have been used for controlling aphids in nasturium in pot experiments performed by Gulf Research and Development Company (Dahle, 1974).

An important new use for benzotriazoles, still probably best considered a minor use, is in waste water treatment for the removal of heavy metals, especially mercury, copper, and cadmium (Okamoto, 1974). In one trial, 3 ppm copper and 1 ppm cadmium were removed from two volumes of waste water at pH 7.85 by shaking for 0.13 hour with one volume of benzene containing 40 ppm benzotriazole (Ochiai et al., 1975). The efficiency of removal of the metals was 100%. On a large scale application, the one remaining problem would be to remove from the metal-free water any residual benzene.

The minor uses for benzotriazole compounds discussed above are summarized in Table 15.

Table 15. Minor Uses for Benzotriazole Compounds

Analytical Chemistry - determination of noble metals

Petroleum Industry - gasoline and oil manufacturing

Biological Applications - antifungal, antiviral agents; pest control

Waste Water Processing - removal of heavy metals

3. Discontinued Uses

Benzotriazole, methylbenzotriazoles, and/or naphthotriazoles used to be regularly present in laundry detergent formulations. The triazoles were included because of their corrosion-inhibiting properties in the presence of phosphate and perborate (Tanner, 1959). With the ban on phosphates in laundry detergent products sold in this country, and the consequent reformulation of these products, benzotriazoles were no longer necessary and are not currently present in these products.

4. Projected or Proposed Uses

There are no proposed uses revealed in the sources examined that differ substantially from the uses described in the previous sections. While consumption of benzotriazoles is expected to grow, projected growth is not attributable at this time to any radically new uses that are presently obvious.

5. Possible Alternatives to Uses

In anticorrosion applications, sodium 2-mercaptobenzothiazole (NaMBT) is probably the major currently manufactured heterocycle which could replace benzotriazole in some applications, although it would not be as effective as benzotriazole at the same concentrations, especially with regard to the protection of copper and copper alloys. NaMBT costs less than the comparable benzotriazole (about 50¢ for NaMBT vs. $1 for sodium tolyltriazole, per pound of 50% aqueous solution) but the benzotriazole is effective in lower concentrations. As a matter of fact, it appears that benzotriazole is likely to make a significant inroad into the large anticorrosion NaMBT market (~6 million pounds per year), rather than the reverse.

In recirculating systems, inorganic anticorrosion replacements for benzotriazoles might include chromates or mercury compounds.

In ultraviolet stabilizer applications, the 2-substituted benzotriazoles compete with and could be replaced by substituted benzophenones, 2-(hydroxyphenyl)-triazines, substituted acrylonitriles (Seymour, 1968), and phenyl salicylate (Rothstein, 1968). Each of these stabilizers would be used at about the same concentration (~0.25% weight of polymer). Recently a number of nickel complexes have been employed as ultraviolet stabilizers (Cesare *et al.*, 1971), including complexes containing benzotriazole-derivative ligands (Mathis, 1975). Complexes with the non-benzotriazole ligands do not have a strong ultraviolet absorption spectrum, but are believed to protect plastics by deactivating the excited states which are part of the degradation chain (Cesare *et al.*, 1971). The presence of nickel in these complexes usually imparts a greenish color to the plastic or fibre substrate. The color is often considered undesirable. Ultraviolet stabilizing agents which act as screens, such as carbon black and other pigments, could replace benzotriazoles, but their application is limited to situations in which the color of the pigment is acceptable.

In photographic applications, 6-nitrobenzimidazole nitrate (Kodak Anti-Fog No. 2) and related imidazoles are often mentioned as antifogging agents. Kodak Anti-Fog No. 2 is useful against fog caused by aldehydes in prehardeners and developers and also against fog caused by the aeration of developers, but it is not considered to be photographically interchangeable with benzotriazole (Anon., 1973).

C. Environmental Contamination Potential

1. General

Benzotriazoles in contact with air, water, or sunlight are likely to be quite stable and persistent. Nevertheless, it is difficult to identify a single source of significant environmental contamination by benzotriazoles. Even when a source of environmental contamination can be identified, it has often been of concern because of another contaminant, and the benzotriazole present is essentially ignored. Thus, when laundry detergents were singled out as an environmental problem, it was because of their phosphate content; no one ever mentioned that benzotriazole was simultaneously being dumped into sewers and lakes. Similarly, the effluent of photofinishers has caused attention because of chromates, thiosulfates, amines, etc., not because very small amounts of benzotriazoles may be present in processing solutions. One must conclude that at least the perceived potential for environmental contamination via benzotriazoles has been small, and the attention paid to it thus far has been negligible.

2. From Production

During the manufacturing of benzotriazole according to the method of Long (1971), the only outputs from the system, aside from the desired benzotriazole product, are the result of the periodic processing of the contents of the crude benzotriazole oil holding tank (see Figure 6). The solid waste from this holding tank probably contains polyazo and polyamine products arising from contamination of the o-phenylenediamine starting material with meta and para isomers. If incinerated, these solids would likely burn to produce CO_2, H_2O and nitrogen oxides which, presumably, would be discharged into the atmosphere. If land-filled, the solids may allow movement of small benzotriazole residues into ground or river waters. The water layer discarded after the alcohol extraction probably contains small amounts of the particular water-insoluble alcohol used (i.e., a butanol or hexanol) as well as traces of the benzotriazole product. The vapors discarded during the steam distillation contain mainly water and the alcohol. In sum, therefore, in normal operation, this process is not likely to be a serious source of environmental contamination by benzotriazole, although more information on disposal of residues is needed. The contamination potential of processes using charcoal filtration would likely arise mainly from periodic disposal of the filtering medium.

Production of the Tinuvin compounds has resulted in some 2-substituted benzotriazoles being detected in the water effluent (Jungclaus, 1977). The trickling filter treatment used at the plant did not reduce the benzotriazole concentrations.

3. From Transportation and Storage

The main hazard in transporting and storing benzotriazole solids is the possibility of a broken container resulting in high concentrations of dust from the chemicals, especially in an enclosed area. Besides a health hazard, dust from benzotriazoles, as dust from wheat in a grinding mill, is an explosion hazard (Dorsett and Nagy, 1968).

4. From Use

In anticorrosion applications, benzotriazoles have little opportunity to contaminate the environment, except by slow leaching or migration processes. Benzotriazole used to protect metals in coating and lacquers probably has a long half life (years) and may enter the environment at an inconsequentially slow rate. Certain high wear items, such as brass handrails, can be a direct source of contact of benzotriazoles with human skin. An even more direct source of human contact with benzotriazoles would be through the use of suntan products containing benzotriazoles as ultraviolet light absorbers.

Benzotriazoles used as ultraviolet absorbers in plastics and fibres can migrate into the environment by movement to the surface of the substrate and evaporation (see Section I-B-1). They can also migrate into the contents of a container made of protected material. Edible oil stored in polyethylene and polyvinyl chloride bottles at 45°C for 10 days contained from 2-20 ppm of Tinuvin type ultraviolet absorbers which migrated from the protected plastic (Uhde and Woggon, 1968). Foods containing oils or fats are more likely to exhibit this kind of contamination than foods free of the fats and oils in which the benzotrizaoles are soluble.

It is probable that no current photographic process presents any significant environmental contamination potential of benzotriazoles. The benzotriazoles used in emulsion manufacturing may, to some extent, leach into processing solutions, but, as mentioned previously, at concentration levels which are insignificant, especially compared to the concentration levels of other photochemicals. Of course, the benzotriazole solid powders could present a hazard to workers in emulsion manufacturing facilities (which same hazard holds for workers exposed to benzotriazoles in polymer and anticorrosion formulation work areas), mainly with respect to the formation of dust.

Biological uses involving sprays or dusts applied in open areas are the one application in which benzotriazoles in use would directly contaminate the environment and possibly food sources. Until the status of benzotriazoles suggested for such uses is clarified with respect to environmental interaction, it is probably wise to restrict widespread use of these compounds for this purpose. Presently, the quantity used for this application appears to be very small.

5. From Disposal

There is little doubt that the major environmental contamination route for benzotriazoles is via spent antifreeze solutions which are periodically poured down drains. Besides this, most benzotriazole compounds used in liquid anticorrosion applications are probably also discarded in sewers. What fraction this represents of benzotriazoles used for anticorrosion, or, indeed, for all applications, is unknown.

The discarding of plastic objects also eventually leads to environmental contamination with UV stabilizers. In the case of biodegradable plastics with water soluble UV protective coatings, the stabilizers get into the environment sooner rather than later.

As mentioned above, the disposal of photographic processing solutions is probably a very minor source of environmental contamination with benzotriazoles compared to other large volume uses such as anticorrosion.

6. Potential Inadvertent Production of Benzotriazoles in Industrial Processes

There is a possibility that benzotriazoles are inadvertently produced during manufacturing operations in the dye industry. The reaction of m and p-phenylenediamines with nitrous acid to produce azo dyes is a very important commercial reaction (Thirtle, 1968). The reaction will also produce some benzotriazole if the phenylenediamine starting material is contaminated with o-phenylenediamine. It is conceivable that a variety of benzotriazoles could be produced during the course of diazotization reactions. However, the presence of small quantities of practically colorless benzotriazoles in an azo dye batch is not likely to be either a manufacturing or an environmental problem, and may even be an advantage if it helps to stabilize the dye to ultraviolet light.

7. Potential Inadvertent Production of Benzotriazoles in the Environment

The chances of benzotriazoles being produced inadvertently in the environment are virtually nil. The possible precursors of triazoles are reactive materials which likely have short half lives if, for example, released into the sea or air. Furthermore, efficient diazotization requires higher temperatures than are normally encountered in the environment. Benzotriazole precursors are sufficiently hazardous in their own right that it is expected efforts would be made to restrict their contact with the environment primarily for that reason, rather than for fear they might react to produce benzotriazoles.

D. Current Handling Practice and Control Technology

1. Special Handling in Use

No special handling is required in the normal use of solid benzotriazole, other than ordinary personal hygiene and the usual precautions when there is a possibility of dust. Benzotriazole is considered to be of very low toxicity and low health hazard (Eastman Kodak Company, 1972). The same is true for methylbenzotriazoles (Sherwin-Williams Co., 1975).

The isopropanol solutions of benzotriazole and methyl benzotriazoles represent a handling problem only insofar as continuous exposure to high concentrations of the solvent can produce a narcotic effect and cause mild eye, nose, and throat irritation. Proper ventilation in the work area and/or respiratory and eye protection are recommended where heavy dust and/or isopropanol vapor are present.

One particular handling practice which should probably be avoided is the distilling of solid benzotriazole under reduced pressure. An unexplained serious detonation of benzotriazole in a vacuum distillation apparatus has been reported (Anon., 1956). The distillation was proceeding normally in a 500 gallon kettle containing 2,000 pounds of benzotriazole at 2 torr and 160°C when the pressure began to rapidly rise. Although emergency devices turned off the heat and opened ventings, detonation occurred shortly thereafter at or above 220°C. The unit had run successfully for four months prior to the explosion, which completely destroyed it and caused $200,000 in property damages. No evidence of azoides, lead compounds, or other detonators were found, nor had extensive lab runs under extreme conditions revealed the potential hazard prior to the accident.

As a group, the Tinuvins are even less toxic than benzotriazole, with the acute oral LD_{50} for the Tinuvins exceeding 5000 mg/kg (Ciba-Geigy, undated) (see Section III-B). Nevertheless, it is recommended that, in accordance with good industrial practice, unnecessary personal contact with these chemicals be avoided. Grounding, venting, and explosion relief provisions are suggested in keeping with good engineering practice to avoid the possibility of static electricity igniting chemical dust (Ciba-Geigy Corp., 1972). Benzotriazole dust is considered a severe explosion hazard (Dorsett and Nagy, 1968), besides being a health hazard if inhaled (see Section III-B). Aside from the potential hazards of dust, no special handling of the Tinuvin compounds is required in use.

Not all benzotriazole compounds are as relatively free of handling hazards as the usual commercial materials. Aldrich Chemical Co. experienced a spontaneous combustion of 1-chlorobenzotriazole while it was being packaged (Hopps, 1971). Their response was to remove it from their product line and recommend extreme caution in handling the compound. (No similar hazard has been reported, nor would be expected, for 5-chloro-1_H_-benzotriazole where the chlorine atom is on the benzene ring rather than the triazole ring). Parish Chemical Company (1976), which currently manufactures 1-chlorobenzotriazole, stores the material at -20°C and finds it stable under these conditions for at least a year.

2. Methods for Transport and Storage

Sherwin-Williams Chemical Company supplies solid benzotriazole and tolyltriazole in fibre drums of 200 pounds net weight. The isopropanol solutions of these compounds and the aqueous solution of sodium tolyltriazole are shipped in 50 gallon steel drums net weight of 500 pounds/drum (Anon., undated). Similar bulk packaging is probably used by Fairmount Chemical Company for solid benzotriazole, 5-chloro-1H-benzotriazole, and 5-methyl-1H-benzotriazole.

Eastman Kodak Company supplies photograde benzotriazole and 5-methyl-1H-benzotriazole to the photographic trade in bottles containing from several ounces to one pound of material (Anon., 1975). Eastman Organic Chemicals (Division of Eastman Kodak Company) supplies practical grade benzotriazole in 100 and 500 gram bottles and occasionally also in bulk lots. Silver benzotriazole is also available (Anon., 1976).

Ciba-Geigy Corporation supplies the Tinuvin compound in standard fibre drum containers with a net weight of 110 pounds. Smaller packages (down to 25 pounds) are available, presumably in bags.

No special storage or transportation methods or precautions are practiced with respect to the solid compounds, with the exception of 1-chlorobenzotriazole which should be stored at low temperatures (i.e., -20°C) and kept away from reducing agents (Parish Chemical Company, 1976). 1-Chlorobenzotriazole slowly decomposes at room temperature. Benzotriazole is heat stable at 330°C, tolyltriazole to 300°C (Anon., undated). Transportation techniques and precautions for isopropanol solutions of benzotriazole would be the same as for any shipment of a relatively volatile, potentially flammable solvent. The 50% aqueous solutions of sodium tolyltriazole are caustic (pH 13.0-13.5). Exposure to large amounts of such solution can cause serious injury. Hence, it must be transported and stored with the care and precautions generally afforded alkaline solutions (Anon., undated).

3. Disposal Methods

Recommended methods for disposal of benzotriazole waste solids are: dispose with normal plant waste (Ciba-Geigy Corp., 1972); bury in a landfill or incinerate (Ciba-Geigy Corp., 1972) [but not in a closed container (Sherwin-Williams Co., 1975)]; or dissolve in a flammable solvent and spray into an incinerator with an afterburner and scrubber (Eastman Kodak Co., 1972). Because the dust is considered an explosion hazard (Sherwin-Williams Co., 1975), disposal should be handled in a way which does not encourage the production of dust. Incineration or ordinary combustion of benzotriazole produces carbon dioxide, nitrogen, and nitrogen oxides. In limited air, combustion products may include carbon monoxide and possibly hydrogen cyanide (Sherwin-Williams Co., 1975).

4. Accident Procedures

Spills of the solids should be swept up promptly. The personnel involved should use approved respirators (Ciba-Geigy Corp., 1972). Local high concentrations of dust should be dampened with water and the area well-ventilated (Sherwin-Williams Co., 1975 a).

Spills of solutions involve accident procedures based mainly on the nature of the particular solvent. The benzotriazoles themselves appear to present no particular hazard in solutions, although aqueous solutions of sodium tolyltriazole are alkaline and should be treated with the same procedures as the spill of any other aqueous caustic.

5. Current Controls and Control Technology Under Development

Present information indicates that benzotriazoles have only been monitored in the effluent of one production plant (Jungclaus, 1977). That plant used a trickling filter treatment plant which exhibited very poor treatment efficiency. Many potential sources of environmental contamination by benzotriazoles (such as discarded antifreeze solutions, water-based cooling fluids, the effluent of photofinishers or film manufacturers) possibly contain many other more serious environmental hazards at far higher concentrations, which explains in part the lack of interest in developing controls for benzotriazoles.

E. Monitoring and Analysis

1. Analytical Methods

Since the middle 1960's, interest in developing analytical methods for benzotriazoles has corresponded to increasing use of these chemicals for anticorrosion purposes. The analytical techniques summarized in Table 16 were devised principally for anticorrosion applications. A limited number of general assay techniques have been reported for benzotriazole compounds used in other than anticorrosion applications.

Benzotriazole is used in metal separations as an analytical reagent. Benzotriazole itself can be determined using the same reactions (Harrison and Woodroffe, 1965). In the presence of excess Ag^+, silver benzotriazole precipitates, is isolated, and weighed. An accuracy of better than 5% is reported for this method with samples containing 100 ppm benzotriazole. No sensitivity data were given, but sufficient sample to contain at least 50 mg benzotriazole is recommended. With this method Keil (1971) reported a standard

Table 16. Methods of Analysis for Benzotriazole

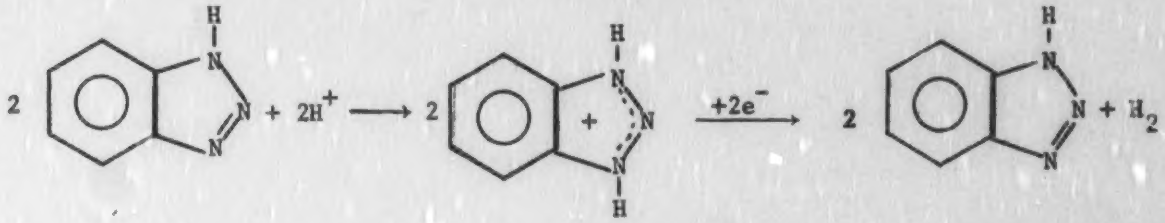
Method	Sensitivity	Relative Error	Principal Features/ Applications	Source
Gravimetric	*	<5%	direct, quantitative/ corrosion inhibitors, plastic stabilizers	Harrison and Woodroffe, 1965; Keil, 1971; Anon., 1975 a
Polarographic	0.4 ppm	~1%	specific, quantitative/ corrosion inhibitors	Harrison and Woodroffe, 1965; Woodroffe and Munro, 1970
Potentiometric titration			/corrosion inhibitors, antifreeze solutions	Anon., 1975 a; Morita *et al.*, 1973
Gas Chromatography			/corrosion inhibitors, antifreeze solutions	Anon., 1975 a; Morita *et al.*, 1973
Spectrophotometric	~0.05 ppm	<1%**	rapid, accurate, quantitative/raw materials and quality control	Anon., 1975 a
Volumetric	200 ppm	~5-10%**	noninstrumental	Anon., 1975 a
GC-MS	1 ppb		ambient water samples	Jungclaus, 1977

*Samples containing 100 ppm benzotriazole were used in developing this technique. Sufficient sample to contain a minimum of 50 mg benzotriazole is recommended.

**Estimates

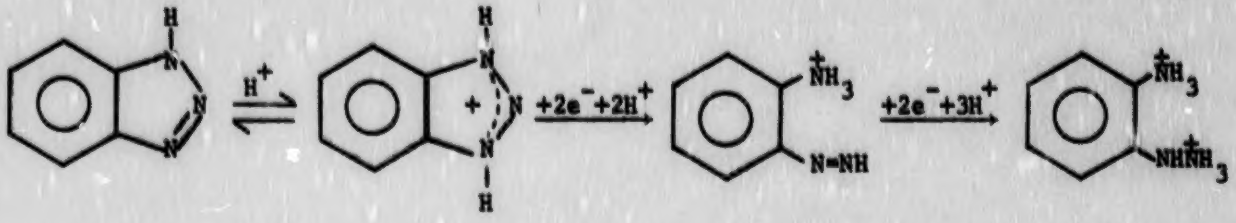
deviation of 1% for samples containing 1-20 mg benzotriazole, and 2-3% for samples containing 0.2-1 mg benzotriazole. Of the various analytical procedures in the literature, this gravimetric method requires the least amount of equipment, but it is relatively slow because starting samples and the silverbenzotriazole must be dried to constant weight (Anon., 1975 a). The ions of zinc, lead, copper, cobalt, nickel, and iron do not interfere. The presence of stannic ion, however, causes high results which can be significantly reduced by complexing the tin with tartrate. Other typical components of glycol-based antifreeze solutions (for which this assay was developed) do not interfere, with the exception of 2-mercaptobenzothiazole (Harrison and Woodroffe, 1965).

Polarographic reduction of benzotriazole in strongly acidic solutions (0.2 M HCl) gives rise to a well-defined wave with $E_{1/2} = -0.98$ volts vs. SCE (Harrison and Woodroffe, 1965). The observed wave was attributed to a one electron reduction of protonated benzotriazole:



A linear variation in diffusion current with benzotriazole concentration was observed over a concentration range of approximately 0.05-2 mM. Other common ingredients in antifreeze solutions did not substantially alter the polarographic wave, nor did the presence of Cu^{+2}, Zn^{+2}, Fe^{+2}, Ni^{+2}, Pb^{+2}, or Sn^{+4} interfere. This method is more rapid and more specific than the gravimetric method described above, if the equipment needed to perform it is available. However, the polarographic method is not suitable for determining trace amounts of benzotriazole in the presence of relatively large concentrations of 2-mercaptobenzothiazole (ca. 0.1-0.2%) unless the two are first separated on an ion exchange resin (Woodroffe and Munro, 1970).

Lund and Kwee (1968) extensively studied the polarography of benzotriazole, its mono and dimethyl derivatives, as well as 1-methyl and 1-hydroxybenzotriazoles. They suggested a reduction mechanism which is considerably different from that of Harrison and Woodroffe (1965). Lund and Kwee attribute the reduction of benzotriazole in acidic solution to a four electron mechanism whose final product is o-aminophenylhydrazine:



While the polarographic data in this work was not gathered specifically in order to develop analytical techniques for the molecules studied, it demonstrates that polarography is a feasible technique for the benzotriazole derivatives investigated.

Bezuglyi et al. (1971) have shown that polarography is suitable for analysis of polyester resins for benzotriazole stabilizers of the Tinuvin family. The stabilizer is extracted for 5-6 hours at room temperature with dimethylformamide. In a background electrolyte of 4 N alcoholic HCl, an $E_{1/2}$ value of 0.71 volts is claimed, but no reference electrode is given. The relative error of the determination is reported to be ±1.7%.

Potentiometry and gas chromatography (with flame ionization detector) have been used by Morita et al. (1973) to determine benzotriazole, 4-methyl and 5-methyl-1H-benzotriazole in antirust paper, antirust fluid, and antifreeze. The potentiometry involves titration with standardized silver nitrate. Recovery of 97-104% is claimed for 2-35 mg samples in 1.5% aqueous solutions of sodium bicarbonate. A variation of this method involves the use of a background solution buffered with sodium acetate (Anon., 1975 a), which is virtually identical to ANSI PH 4.204-1972.

The fastest method for assaying the purity of benzotriazole and methylbenzotriazole compounds as raw materials is the spectrophotometric technique of the Sherwin-Williams Company (Anon., 1975 a), which depends on the characteristic ultraviolet absorption of these compounds at 274 and 276 nm, respectively. This method is not only rapid, it is highly sensitive (~0.05 ppm).

In the absence of instrumentation for the electrometric or spectroscopic techniques, benzotriazole and methylbenzotriazole compounds can be determined in a concentration range of 200-2000 ppm by a volumetric method which is a variation on the Volhard method for chloride (or silver ion) (Anon., 1975 a). The benzotriazole sample reacts with a known volume of standardized silver nitrate solution and the excess silver ion is titrated with ammonium thiocyanate to the pale orange end point.

Hites and his coworkers at MIT (Jungclaus, 1977) have used a gas chromatography-mass spectrometry (GC-MS) technique for detecting the 2-substituted benzotriazoles in wastewater effluents and in downstream water and sediments. The method consisted of methylene chloride extraction followed by GC-MS analysis and was sensitive down to approximately 1 ppb.

2. Current Monitoring

Two of the Tinuvin compounds, 2-(2'-hydroxy-5'-methylphenyl)-benzotriazole and 2-(2'-hydroxy-3',5'-di-t-amylphenyl)-benzotriazole, have been detected in the effluents from a specialty chemical plant located on the Pawtuxet River in Rhode Island (Jungclaus, 1977). The two compounds where found in concentrations of 2.9 ± 1.4 and 2.4 ± 0.85 ppm, respectively, in wastewater; 0.053 ± 0.007 and 0.038 ± 0.006 ppm, respectively, in river water; and 76 ± 52 and 15 ± 6 ppm, respectively, in sediment. These compounds were detected in samples collected from the most distance sampling site (approximately 4 miles).

No other ambient or effluent monitoring studies have detected benzotriazoles.

III. Health and Environmental Effects

A. Environmental Effects

1. Persistence and Biodegradability

On the basis of the chemistry of benzotriazoles (see Section I-B), these compounds are probably persistent in the environment. The fact that the Tinuvins have been detected four miles downstream from a product plant confirms that suggestion, at least for the 2-substituted benzotriazoles. Benzotriazole does not oxidize or hydrolyze under environmental conditions. Studies of photolytic reactions of benzotriazoles under environmental conditions are not available. However, benzotriazole (in a methanol solution) has been irradiated with 300 nm light and some ring breakage occurs (Boyer and Selvarajan, 1969). Nevertheless, the mechanism for the use of benzotriazoles as UV stabilizers (absorb light and release it as heat without photochemical reactions) suggests that these compounds are probably stable under sunlight irradiation.

The potential of benzotriazole to interfere with the seed activity in the standard 5-day BOD test has been briefly studied by Quinn (1972). He determined the total bacterial count in the seeded dilution waters to which various concentrations of benzotriazoles were added (no other carbon source added). The presence of benzotriazole was found to cause an increase in the number of viable microorganisms over those found in the blank control (Table 17). The author concluded that the benzotriazole may be acting as a growth promoter. A similar enhancement in the cell numbers would, however, be expected if benzotriazole served as a carbon source for the microorganisms. This might suggest that benzotriazole is susceptible to attack by sewage microorganisms. The evidence is, however, fragmentary and further work is needed to ascertain the biodegradability of benzotriazole. A similar study on tolyltriazole (Quinn, 1973) at concentration levels of 0.2 - 20 mg/ℓ concluded that tolyltriazole does not show any sizable oxygen demand over that of controls in this concentration range. As in the previously cited study, the purpose of this work was to examine the effect of the compound on the natural flora in a wastewater treatment plant or receiving stream, rather than to specifically consider the biodegradability of benzotriazoles.

Table 17. Survival of Wastewater Microorganisms in Contact with Benzotriazole (Quinn, 1972)

Benzotriazole Concn. in Seeded Dilution Water (ppm)	Total Colony Count/mℓ After 5 Days Incubation*
0	151,000
0.66	207,000
3.3	217,000
6.6	183,000
13.2	164,000

* Initial colony count/mℓ = 54,570

2. Environmental Transport

Very little experimental data are available concerning environmental transport and intermedia distribution of benzotriazole and its derivatives. The low vapor pressure of these compounds (Table 2) suggests that they will not enter and distribute in the atmosphere to a significant extent. Also, their rate of evaporation from water bodies to the atmosphere will be slow, as predicted, using the approach developed by MacKay and Leinonen (1975). For example, the calculated half life for 1H-benzotriazole at less than saturation concentration in a square meter of water would be 438 hours. (For comparison, benzene's half life is 4.81 hours.) The equation for predicting approximate rates of evaporative loss of low solubility contaminants in an air-water system is based on the assumption that the water column undergoes continuous mixing, that the compound is present in true solution, and not adsorbed, complexed, etc. Recently, Dilling et al. (1975) have found a discrepancy between experimentally determined evaporation half lives for certain chlorinated hydrocarbons and values calculated according to the equation developed by MacKay and coworkers. In view of this, it is suggested that the calculated value be treated only as a rough approximation.

In view of the appreciable water solubility of some benzotriazoles (e.g., 1H-benzotriazole, tolyltriazole), it may be expected that they will migrate through soil and eventually make their way to ground water. Other virtually water insoluble benzotriazole derivatives (e.g., Tin-P, Tin-326, Tin-327), have been shown to concentrate in river water sediments at concentrations almost a thousand times the concentration found in river water (Jungclaus, 1977).

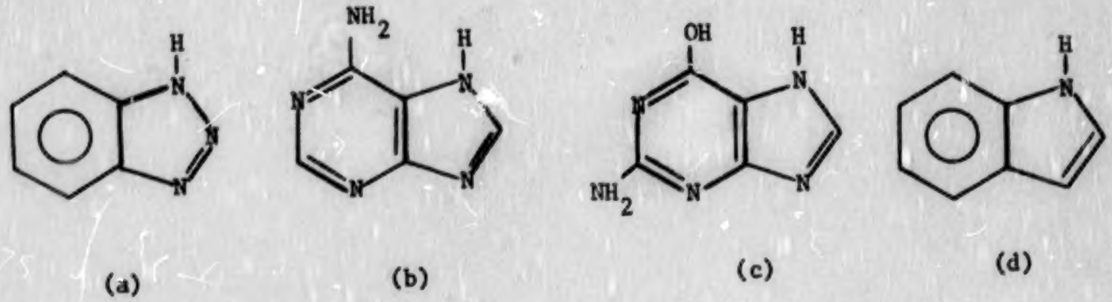
3. Bioaccumulation and Biomagnification

Bioaccumulation and biomagnification potential of benzotriazoles has not been reported in the literature. Neely et al. (1974) have reported a linear relationship between octanol-water partition coefficients and bioconcentration of chemicals in trout muscle. Using the equation of the straight line of best fit, derived by Neely et al. (1974), the bioconcentration factor of 1*H*-benzotriazole (log octanol-water partition coefficient, 25°C = 1.34) is calculated to be approximately 7. The log partition coefficient of 1*H*-benzotriazole falls outside the range of the data of Neely *et al*. (1974). Consequently, less confidence must be placed on the prediction.

Biomagnification potential, which refers to concentration of a compound through the consumption of lower organisms by higher food chain organisms with a net increase in tissue concentration, can be predicted for benzotriazoles on the basis of their water solubility. Metcalf and Lu (1973) have found ecological magnification of several chemicals (concentration in organisms/concentration in water) in their model aquatic ecosystem follows a straight line relationship with water solubility. From this relationship, the ecological magnification for 1*H*-benzotriazole and tolyltriazole is calculated to be <1, which suggests that these compounds will not biomagnify to a significant extent in food chain organisms. Other benzotriazoles, such as Tin-P, Tin-326, Tin-327, and Tin-328, which are virtually insoluble in water, may, however, be expected to biomagnify considerably more.

B. Biological Effects

Interest in the biological properties of benzotriazole and its derivatives has been prompted, in part, by their general structural similarities to naturally occurring and endogenously important substances in mammalian systems. Experimentally, the benzotriazoles have demonstrated antagonistic activity toward utilization of the purines, adenine and guanine, and also show properties similar to indole. These structures are presented in Figure 9.



(a) (b) (c) (d)

Figure 9. Naturally Occurring Chemical Structures Compared to Benzotriazole (a) Benzotriazole; (b) Adenine; (c) Guanine; (d) Indole

The actions of benzotriazoles when introduced into biological systems may lead to interference with endogenous purine utilization and the consequent inhibition of protein synthesis. It is suggested that certain benzotriazoles could act to inhibit enzymes involved in the synthesis of nucleic acid (RNA or DNA) or perhaps may actually be incorporated into the molecule itself, and thereby cause abnormal function. Studies conducted with another related purine antagonist, 8-azaguanine, have shown that it can inhibit growth in both normal and malignant cells (Kidder et al., 1949; Gellhorn et al., 1950). This occurs by incorporation into the nucleic acids (Smith and Matthews, 1957; Mandel, 1957, 1961) and causes inhibition of protein synthesis (Chantrenne and Devreux, 1958, 1960).

Because they have similar properties to indole, the benzotriazoles have been investigated for pharmacologic activity, particularly with regard to effects on the central nervous system. It is known that unsubstituted indole will produce convulsions originating in the spinal cord and subthalamic areas of the brain, and benzimidazole (3-azaindole) will cause a transient flaccid paralysis due to interneuronal depression (Adler and Albert, 1963).

Benzotriazole and its derivatives have not been extensively studied for biological activity, especially in recent years. For this reason, subsequent sections in this report will present the available data on a number of benzotriazole compounds which do not have significant commercial importance or environmental contamination potential. In this manner, however, it may be possible to make cautious extrapolations of data from related compounds in order to provide a reasonable indication of biological consequence for similar substances where specific data are lacking. In addition, a thorough examination of the properties of a particular chemical and its substituted derivatives may indicate the potential harm that may result from environmental alterations of the parent compound.

1. Toxicity and Clinical Studies in Man

A search of the available literature indicates that occupational and epidemiologic studies have not been conducted for benzotriazole or its methyl-substituted derivatives, nor have any poisoning incidents been reported. Eastman Kodak Company (1975) has stated that their experience in the manufacture of benzotriazole and handling of solutions containing it "has generally been very good."

Limited toxicity testing in humans has been conducted with two benzotriazole-derivative ultraviolet stabilizers, Tinuvin-P and Tinuvin-327 (Ciba-Geigy, 1976). Repeated insult patch tests with a 0.5% solution of Tinuvin-327 were performed on 55 male and female subjects. The treatment failed to induce either primary skin irritation or allergic sensitization in all of the subjects.

Tinuvin-P was patch tested in human females as either a 0.1% solution (50 subjects) or a 0.5% solution (50 subjects) dissolved in dimethyl phthalate. The experimental protocol consisted of a 24-hour application three days per week for three weeks (total of ten applications), followed by a two-week rest period and then a 48-hour challenge application. This treatment did not cause irritation or sensitization in any of the subjects.

Ciby-Geigy (1976) also patch tested Tinuvin-P in 25 human males as a 25% formulation in petrolatum. The material was applied to abraded skin in five 48-hour applications, with one-day intervals between exposures. Following a two-week rest period, a new area of abraded skin was challenged with a 10% formulation of Tinuvin-P in petrolatum for 48 hours. Sensitization was not induced in any of the subjects by this treatment.

In addition to being tested for skin irritancy and sensitizing potential, Tinuvin-P was evaluated for phototoxicity in humans (Ciba-Geigy, 1976). The chemical, when applied to the backs of ten male subjects for 24 hours, did not exacerbate the production of erythema resulting from exposure to ultraviolet light.

Ciba-Geigy (1976) has stated that no cases of occupational poisoning have occurred among employees engaged in the manufacture of Tinuvin-327 and products which contain it. Likewise, they have noted that no symptoms of poisoning in man have been reported following the ingestion of Tinuvin-P.

2. Effects on Non-Human Mammals

a. Absorption/Excretion Studies

There are no reports in the scientific literature directly concerned with the absorption or elimination of benzotriazole and its derivatives in animal systems. It is possible, however, to draw a limited number of inferences regarding the likelihood of these compounds being absorbed. It is well-known that the relationship between toxicity and degree of absorption for any foreign compound is largely dependent upon its molecular structure, lipid solubility, degree of ionization, and vapor pressure. Therefore, based on these parameters, a reasonable prediction of the ease of entry into the circulation for benzotriazole can be constructed.

When exposure to foreign substances occurs by oral ingestion, diffusion across the gastric epithelium will be greatest for lipid-soluble neutral molecules (i.e., compounds having a high lipid/water partition coefficient and which are mainly undissociated at the pH of the gastric contents). The absorption and rate of passive diffusion for both organic acids and bases will decrease with increasing ionization of the undissociated moiety. Consequently, the absorption of most chemicals will be favored by a pH that increases the proportion of the undissociated form. For the most part, this relationship also holds true for absorption of foreign substances through the skin, which also acts as a lipoidal membrane and is most readily penetrated by lipid-soluble neutral molecules (Schanker, 1964).

The degree of ionization of xenobiotics is a function of both pH conditions and the pKa value for the particular chemical. The pKa value is an expression of the pH at which 50% of the compound will be in the dissociated form and 50% in the undissociated form. Schanker (1964) has noted that gastrointestinal absorption was greatest for acidic compounds having pKa values greater than 3 and basic compounds with pKa values less than 8.

The pKa and lipid solubility of benzotriazole, a weak acid, were determined by Albert _et al_. (1948) and Adler and Albert (1963). Table 18 presents the physical properties of benzotriazole and indicates that, as a weak acid, fairly rapid absorption of benzotriazole is likely to occur across the intestinal epithelium (pH 6.5). Furthermore, at blood pH (7.4) Adler and

Albert (1963) predicted a low degree of ionization for benzotriazole (.0002%) which suggests that it would easily pass into the central nervous tissue. This prediciton is supported by toxicologic evidence (see Section III-B-2-b) which confirms its action on the central nervous system.

Table 18. Physical Properties of Benzotriazole (Adler and Albert, 1963)

pKa†	Lipid/Water* Distribution Ratio	% Ionized at pH 7.4
8.57	3.0	.0002

* Oily phase used was oleyl alcohol.
† Taken from Albert _et al_. (1948).

Adler and Albert (1963) noted that benzotriazole is much less lipid-soluble than the related compounds indole or benzimidazole (lipid/water distribution ratios of 85 and 16.4, respectively). Nevertheless, the organosolubility of benzotriazole is apparently sufficient to promote rapid penetration into the brain, as evidenced by its central effects (see Section III-B-2-b). Supporting experimental data are not available, however, since the transport and distribution of benzotriazole have not been studied.

b. Metabolism and Pharmacology

The biological activity of any drug or foreign compound in the mammal will be dependent upon the rate at which the substance is metabolically transformed into water-soluble inactive products. In many instances, however, enzymatic conversion of a substance in the body produces an active metabolite which accounts for the observed effects of the chemical. For benzotriazole and its derivatives, there have been no studies conducted to determine their metabolic products or the primary eliminative routes in animal systems.

The only indication of metabolic inactivation of the benzotriazoles is by noting their duration of action when administered to experimental animals at toxic doses.

Central Nervous System Effects

Evidence that benzotriazole and its derivations produce selective pharmacologic effects on the central nervous system was provided by Domino _et al_. (1952). Albino mice (18 to 24 grams) were given benzotriazole or one of its derivatives by intravenous injection and observed for the development of paralysis. A median paralyzing dose (PD_{50}), measured as the dose to produce a loss of the righting reflex in 50% of the experimental animals, was determined (Table 19).

Table 19. Median Paralyzing Doses of Benzotriazole Derivatives on Intravenous Administration to White Mice (Domino _et al_., 1952)

Compound	PD_{50}*
1_H_-Benzotriazole	55±3
1-Methylbenzotriazole	230
1-Ethylbenzotriazole	50

* All doses are given in mg/kg ± standard error. Values without standard error are approximate.

Mice treated with benzotriazole immediately displayed an increase in activity (running and squeaking) and within a few seconds became ataxic, culminating in loss of the righting reflex. A semi-flaccid paralysis was seen, which began in the hindlimbs and was reversible within a few minutes.

Respiration in the mice was increased, but lethal doses of benzotriazole decreased the amplitude of respiratory movements and caused death by respiratory arrest. The actions of benzotriazole were qualitatively similar to those produced by the related compound benzimidazole, which was somewhat less potent.

The 1-methylbenzotriazole derivative was considerably less potent than the unsubstituted compound and produced respiratory depression, hyperreflexia, and tremors. Substituting a 1-ethyl group in benzotriazole produced a compound with the highest potency of the three tested, which caused respiratory depression in paralyzing doses.

The site of action for the benzotriazole derivatives was established as being in the central nervous system, rather than peripheral, by testing the compounds for curare-like effects (Domino et al., 1952). Benzotriazole was administered in a dose of 1 gm/kg into the ventral lymph sac of frogs. During the benzotriazole-induced paralysis, responses of the gastrocnemius muscle were observed to indirect (nerve) and direct (muscle) electrical stimulation. Whereas curare, a peripheral nervous system poison, would block electrical stimulation of muscle contraction, a centrally-acting agent would not. Stimulation of the sciatic nerve in benzotriazole-poisoned frogs resulted in contraction of the gastrocnemius muscle, even though the animal was in a state of flaccid paralysis. Therefore, the observed paralysis was of central origin since benzotriazole treatment did not impair conduction in peripheral nerves (sciatic) or block transmission across the neuromuscular junction.

In later studies conducted by Adler and Albert (1963), benzotriazole was investigated for pharmacologic action because of its structural relationship to naturally occurring indole derivatives. Male albino mice

(15 to 20 grams) were treated with benzotriazole by intraperitoneal injection in groups of 8 to 10 mice at four or five dose levels. A median effective dose (ED_{50}) was calculated for the point at which: (1) 50% of the animals lost the ability to right themselves when placed on their backs, and (2) the onset of mild clonic-tonic convulsions. For benzotriazole, the ED_{50} was calculated at 250 mg/kg body weight.

The toxic effects of benzotriazole in small doses were manifested by the sudden onset of occasional clonic seizures (about ten per minute) superimposed on a flaccid paralysis which abolished the righting reflex. With almost equal frequency, larger doses produced death either by tetanic tonic convulsions or respiratory failure. These mixed effects demonstrated that benzotriazole may produce selective central nervous system stimulation, depression, or both at the same time. Other related compounds were either exclusively stimulatory (indole) or depressant (benzimidazole) in their actions on mice (Adler and Albert, 1963).

Effects on Experimental Tumors

Screening programs for the detection of compounds with antitumor effectiveness have been conducted with numerous animal tumor systems, both *in vivo* and *in vitro*. Benzotriazole was tested against several animal tumors *in vivo* by the Cancer Chemotherapy National Service Center (CCNSC) (Anon., 1958). Three experimental tumor systems were employed: (1) Sarcoma 180 (S180) in Swiss albino mice, (2) mammary adenocarcinoma 755 (Ca755) in C57-DBA hybrid mice, and (3) lymphoid leukemia (L1210) in C57-DBA hybrid mice. Screening results are presented in Table 20 and demonstrate that benzotriazole was found to be tumor inhibitory against Ca755.

Table 20. Effect of Benzotriazole Against Various Experimental Tumors by Repeated Intraperitoneal Injection

CCNSC Screening Results*			
S180**	Ca755	L1210	Other Screening Data†
-(250)	+(225)	-(250)	0/3

* Symbols: - = no significant tumor inhibition or increase in survival time (for L1210); + = significant tumor inhibition in at least two trials.

† Literature survey of animal tumor reports other than CCNSC tests. The numerator indicates the number of "positive" reports. The denominator indicates the number of reports in the literature survey.

** Number in parentheses indicates the highest nontoxic dose treated.

Inhibition of tumor growth by benzotriazole treatment was also shown in studies conducted by Tarnowski and Bates (1961). Their technique involved the direct incubation of tumor fragments with benzotriazole solutions followed by implantation into susceptible hosts to determine viability of the treated fragments. Nelson mouse ascites tumor cells, carried in Swiss albino mice, were collected six to seven days after tumor implantation and diluted to contain 10^8 cells per ml. The cell suspension was incubated with benzotriazole at concentrations ranging from 0.1 to 10 mg/ml for a 24-hour period. A portion of the incubated suspension, containing 1×10^7 cells, was then injected subcutaneously into mice. A record was kept of the number of tumor inocula growing in each subcutaneous location (tumor takes) after one, two, and three weeks. Their results, summarized in Table 21, indicated that benzotriazole produced moderate to marked inhibition of tumor growth at incubation concentrations of 1 and 10 mg/ml.

Table 21. Bioassay of Suspensions of the Nelson Mouse Ascites Tumor Treated with Benzotriazole *In Vitro* (Tarnowski and Bates, 1961)

Dose mg./ml.	Number of Exposures	First Week		Second Week		Rating†
		Takes	AWC*	Takes	AWC	
0	2	10/10		10/10		
.1		10/10	+3.6	10/10	+2.2	—
1		0/10		3/10		+
10		0/10		0/10		++

* AWC = % average weight change

† Rating: — = inactive (75 - 100% growing tumor inocula); + = moderate inhibition (25 - 49% growing tumor inocula); ++ = marked inhibition (0 - 24% growing tumor inocula)

Negative results on tumor inhibition by benzotriazole and two of its derivatives were obtained by Gellhorn et al. (1953). Mice bearing either mammary adenocarcinoma 755 or Crocker Sarcoma 180 were treated with repeated injections of benzotriazole or its 6-chloro- or 6-nitro-derivative. At the dose levels employed in this study, tumor inhibition was not seen, although death and decreased body weight gains were noted in certain groups (Table 22).

Negative results were also obtained by Stock et al. (1960) when benzotriazole was tested against Sarcoma 180 in Swiss female mice. Tumor fragments were cut from portions of a donor tumor and implanted subcutaneously into the axillary region of five mice. Twenty-four hours after implantation, therapy was initiated with each mouse receiving 13 daily intraperitoneal injections of benzotriazole at 400 mg/kg body weight. No deaths resulted and tumor growth was not inhibited by this treatment.

Although the evidence is not clear, it appears that benzotriazole may possess a certain degree of tumor inhibitory activity. This activity may be related to its structural similarity to the purines which results in a disruption of nucleic acid metabolism in rapidly dividing tumor cells. Inhibitory effects on bacteria (see Section III-B-6) and tissue cultures of normal and malignant cells (see Section III-B-7) lend support to the theory that benzotriazole is capable of disrupting fundamental cellular processes. Furthermore, mutagenic and inhibitory activity by substituted benzotriazoles on bacterial mutants having different purine requirements (see Section III-B-2-g) suggests that certain benzotriazole derivatives can affect the utilization of natural purines.

Uncoupling of Oxidative Phosphorylation

Several derivatives of benzotriazole have been found to be effective uncouplers of oxidative phosphorylation in rat liver mitochondria (Parker, 1965). This effect is identical to that produced by 2,4-dinitrophenol,

Table 22. Negative Cancer Chemotherapy Results in Mice (Gellhorn *et al.*, 1953)

Compound Name	Tumor	Age of Tumor Days	Mouse Strain	No. of Deaths/ No. of Test Animals	Dose mg/kg/day	Av. Wt. Change: treated/ controls	No. of Treatments	Vehicle
Benzotriazole	755	1-2	C57	1/40	50-150	-6/+5	11-15	H_2O
	S180	1	Paris	0/20	50	0/+4	9	H_2O
6-Chlorobenzotriazole	755	2	C57	1/30	50	0/-3	11-15	NaOH to pH8
	S180	1	Paris	0/20	50	+2/+4	9	NaOH to pH8
6-Nitrobenzotriazole	755	2	C57	4/30	50	-6/-5	11-15	NaOH to pH8
	S180	1	Paris	0/20	50	+2/+4	9	NaOH to pH8

a classic uncoupler. However, the tetrachloro derivative of benzotriazole is a much more potent uncoupler than 2,4-dinitrophenol (see Section III-B-7-c). Accompanying the demonstration of in vitro uncoupling in rat liver mitochondria by 4,5,6,7-tetrachlorobenzotriazole, 5-chloro-4-nitrobenzotriazole, and 5-nitrobenzotriazole was the observation that these compounds, when given in lethal doses to rats, produced an early onset of rigor mortis which was complete at death. This phenomenon is characteristic of the pharmacologic action of other uncouplers such as 2,4-dinitrophenol.

c. Acute Toxicity

The acute toxicity of a chemical substance refers to the adverse physiologic effects produced by single dose exposure. Although the measurement of an LD_{50} (dose required to cause death in 50% of an experimental population) is a valuable tool in determining the consequences of overexposure or accidental poisoning, such investigations bear little resemblance to environmental exposure situations. However, the relationship between varying acute doses and the effects produced in a group of animals can be used to construct a graphical representation (dose-response curve) which reveals several important parameters in characterizing a chemical toxicant. Indications of toxic potency, maximum effect, response threshold, sensitivity, and biological variability can all be derived from properly designed acute toxicity studies.

It should be kept in mind that a number of factors can modify the effects of a chemical substance, leading to qualitative and quantitative discrepancies in experimental results. Among the most important modifying factors are species, strain, sex, age, route of administration, rate of biotransformation, tolerance, genetic influence, and chemical interactions.

Only a limited number of acute toxicity studies have been conducted with benzotriazole derivatives in laboratory mammals. These studies have been restricted to investigations involving either rats, mice, or rabbits.

Acute Oral and Parenteral Toxicity

A summary of the published data regarding the median lethal doses (LD_{50}) for various benzotriazole derivatives by oral and parenteral administration is presented in Table 23. The data are not entirely consistent, nor do they indicate a clear difference in species susceptibility between the rat and mouse. A comparison of LD_{50} values for benzotriazole in the mouse by intravenous (238±16 mg/kg) and intraperitoneal (500-1000 mg/kg) administration indicates that considerable detoxification may result due to first-pass metabolism in the liver.

It is also apparent that the addition of bulky substituents to the benzotriazole moiety, as with Tinuvin-P and Tinuvin-327, considerably decreases acute toxicity. This effect may be due, in part, to gastrointestinal factors and bacterial action, since it has been shown that intraperitoneal administration of Tinuvin-327 markedly enhances toxicity when compared to the oral route (Table 23).

An indication of dose-response relationships for benzotriazole and tolyltriazole (a mixture containing predominantly 4-methyl and 5-methylbenzotriazole) can be derived from data supplied by the Sherwin-Williams Company (1976). The compounds were administered orally to four groups of ten rats (five male and five female) which were observed for 14 days after treatment. The dose levels and responses are summarized in Table 24.

When the data from Table 24 are portrayed graphically according to the method of Litchfield and Wilcoxon (1949), several relationships become

Table 23. Acute Toxicity of Benzotriazole and Derivatives in Laboratory Rodents

Compound	Animal	Route of Administration*	Dose (mg/kg)	Response	Reference
1-H-Benzotriazole	Rat (20 male and 20 female)	Oral	560	LD_{50}	Sherwin-Williams Co., 1976
	Rat	Oral	500	Minimum lethal dose	Christensen and Luginbyhl, 1975
	Rat	Oral (in H_2O)	>5000	Lethal dose	Eastman Kodak, 1976
	Rat	I.P. (in organic solvent)	500-900	Lethal dose	Eastman Kodak, 1975
	Mouse (Swiss-Webster males; 4 or 5 groups of 8-10 mice each)	I.P. (in oil)	500	LD_{50}	Adler and Albert, 1963
	Mouse	I.P.	1000	LD_{50}	Smith _et al._, 1963
	Mouse (Harlan)	I.V.	238±16	LD_{50} and standard error	Domino _et al._, 1952
2-(3',5'-di-tert-Butyl-2'-hydroxyphenyl)-5-chlorobenzotriazole (Tinuvin 327)	Rat (male and female)	Oral	>5000	LD_{50}	Ciba-Geigy, 1976
	Mouse (male and female)	Oral	>5000	LD_{50}	Ciba-Geigy, 1976
	Mouse	I.P.	3000	LD_{50}	Ciba-Geigy, 1976
1-Ethylbenzotriazole	Mouse (Harlan)	I.V.	125	LD_{50}	Domino _et al._, 1952
2(2'-Hydroxy-5'-methylphenyl)benzotriazole (Tinuvin P)	Rat (male and female)	Oral	>5000	LD_{50}	Ciba-Geigy, 1976
	Mouse (male and female)	Oral	>5000	LD_{50}	Ciba-Geigy, 1976
1-Methylbenzotriazole	Mouse (Harlan)	I.V.	375	LD_{50}	Domino _et al._, 1952
5-Methyl-1_H_-benzotriazole	Rat	Oral	1600	LD_{50}	Eastman Kodak, 1975
	Mouse	Oral	800	LD_{50}	Eastman Kodak, 1975
Tolyltriazole (mixture containing 4-Methyl- and 5-Methylbenzotriazole)	Rat (20 male and 20 female)	Oral	675 (535-851)	LD_{50} with 95% confidence limits	Sherwin-Williams Co., 1976

*Symbols: I.P. = intraperitoneal; I.V. = intravenous.

Table 24. Acute Oral Toxicity to Rats of Varying Doses of Benzotriazole or Tolyltriazole (Sherwin-Williams Co., 1976)

Dose (mg/kg)	Benzotriazole				Tolyltriazole			
	Day of Death			Total Dead / Total Treated	Day of Death			Total Dead / Total Treated
	0	1	2		0	1	2	
1001	--	--	--	--	10/10	0	0	10/10
795	4/10	6/10	0	10/10	6/10	1/10	0	7/10
632	0/10	7/10	0	7/10	1/10	2/10	0	3/10
502	0/10	2/10	2/10	4/10	3/10	0	0	3/10
398	0/10	0	0	0/10	--	--	--	--

evident (Figure 10). The steep slopes of the dose-response curves for benzotriazole and tolyltriazole immediately suggest a sensitive population with minimal variability. Benzotriazole is obviously slightly more potent than the methylated derivative. However, for both compounds the margin of safety between non-toxic and lethal doses is very small. Since the slopes of both dose-response curves are similar, it can be predicted that the mechanism of toxic action may be the same for both chemicals.

Acute Dermal Toxicity

Investigations conducted by the Sherwin-Williams Company (1976) indicated that neither benzotriazole nor tolyltriazole is significantly toxic to rabbits by dermal exposure. The compounds were each applied to the clipped skin of five female rabbits and to the clipped and abraded skin of five female rabbits. The material remained under occlusive bandage for 24 hours, after which time the skin was washed with water and daily observations made for two weeks.

At 2000 mg/kg of body weight benzotriazole produced no deaths from dermal exposure in any of the rabbits. Three of the five rabbits having abraded skin developed a well-defined but transitory erythema on day two of the study. Edema was absent in all test animals. Animals, on the average, continued to gain weight throughout the experimental period (average = +83%), but the absence of untreated control rabbits prevented a quantitative comparison of the rates of body weight gain. Histopathologic examinations were not conducted upon sacrifice of the animals.

Results of treating rabbits by dermal application of tolyltriazole at 2000 mg/kg of body weight were essentially identical to those obtained with benzotriazole. Edema was absent in all animals; three of five

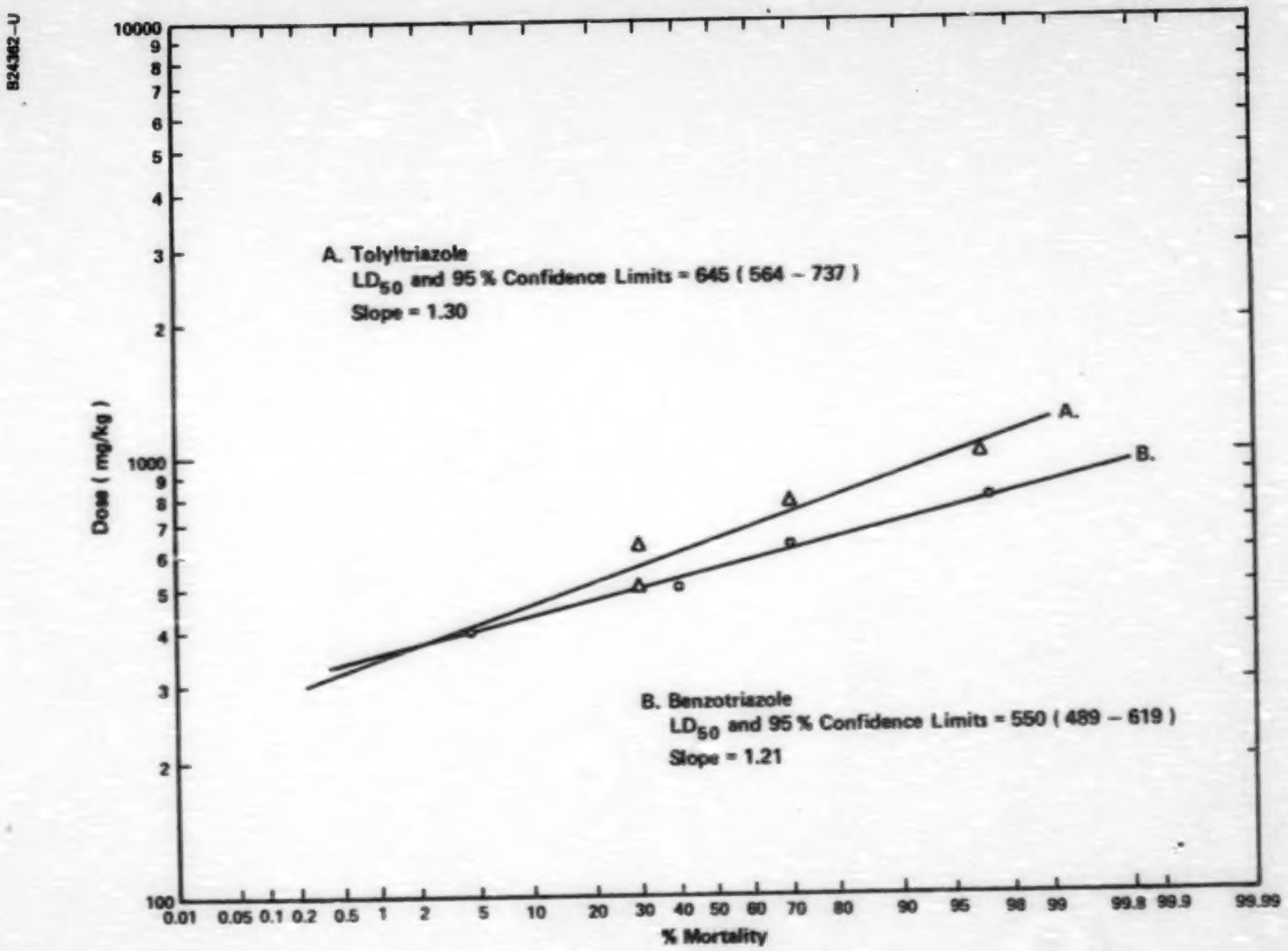


Figure 10. Acute Toxicity in Rats Treated Orally with Various Doses of Benzotriazole or Tolyltriazole

rabbits with abraded skin displayed very slight erythema which disappeared after three days. Four of the ten experimental rabbits showed no gain in body weight over the 14-day test period; one animal suffered a 3% decrease in body weight. Once again, the absence of untreated control animals prevented quantitative comparisons. Histopathologic analyses of tissues were not conducted.

Eastman Kodak Company (1975) evaluated the toxicity of 5-methyl-1H-benzotriazole in guinea pigs, when applied as a moistened solid to the skin under occlusive bandage for 24 hours. Slight skin irritation was produced by the treatment. The dermal LD_{50} for the compound exceeded 1.0 gm/kg of body weight in the guinea pig.

Primary Skin Irritation

Benzotriazole and tolyltriazole were evaluated for primary skin irritation in adult female New Zealand albino rabbits (Sherwin-Williams Company, 1976). One-half gram of chemical was applied to a one-inch square area of clipped skin on the backs of twelve rabbits for each compound. Six of the rabbits in each group were exposed to the compound on abraded skin. The treated area was covered with tape for 24 hours, after which time the tape was removed and skin reactions evaluated. A second evaluation was made 72 hours after the initial treatment. In all cases, the rabbits were completely free of adverse skin reactions (edema or erythema) resulting from the chemical exposure.

Primary Eye Irritation

Experimental evidence has been presented by Sherwin-Williams Company (1976) which indicated that both benzotriazole and tolyltriazole were irritating to the eyes of rabbits.

Six female albino New Zealand rabbits were used in evaluating each chemical. Animals were treated by instilling 100 mg of chemical in one eye of each rabbit, the other eye serving as a control. Ocular reactions were graded at 24, 48, and 72 hours and 14 days. At 24 hours, the eyes were also stained with fluorescein and examined under ultra-violet light to detect corneal damage. Results obtained with both chemicals are summarized in Table 25. These results indicate that benzotriazole and tolyltriazole present significant hazards to the eye.

The primary eye irritation potential of 5-methyl-1H-benzotriazole has been evaluated by Eastman Kodak Company (1975). When "several crystals" were applied to the eyes of a rabbit, moderate irritation, injection of the iris, and staining of the cornea were noted. If unwashed, the treated rabbit eye still displayed edema and erythema 48 hours after application. The washed rabbit eye returned to normal after 24 hours; the unwashed eye recovered within two weeks. These results are somewhat consistent with those obtained using tolyltriazole and thereby confirm the eye irritation potential of these chemicals.

An evaluation of Tinuvin-P for eye irritation revealed that the compound was "minimally irritant" and produced mild conjunctival reactions in two of six treated rabbits (Ciba-Geigy Corp., 1976).

Acute Inhalation Toxicity

A report on the inhalation toxicity of benzotriazole to rats indicated that the substance may present a severe respiratory hazard (Sherwin-Williams Company, 1976). Fifty male rats, in five groups of ten animals each, received a single three-hour exposure to a benzotriazole aerosol at one of five different concentrations. Exposure levels and mortality data are presented in Table 26. Data were not supplied on the parameters of aerosol particle size or relative humidity.

Table 25. Primary Eye Irritation by Benzotriazole and Tolyltriazole (Sherwin-Williams Co., 1976)

TEST	BENZOTRIAZOLE*		TOLYLTRIAZOLE*	
	No. Observed/ No. Exposed	Reaction	No. Observed/ No. Exposed	Reaction
Cornea	1/6	Translucent areas of opacity	2/6	A diffuse area of corneal opacity
	1/6	No details of iris visible	3/6	Discernible translucent areas of opacity
	4/6	Complete corneal opacity	1/6	No details of iris visible
	6/6	Fluorescein examination positive	6/6	Fluorescein examination positive
Iris	5/6	Moderate circumcorneal injection	4/6	Moderate circumcorneal injection
Conjunctival Redness	4/6	Diffuse crimson red	4/6	Diffuse crimson red
	2/6	Diffuse beefy red	2/6	Diffuse beefy red
Chemosis	2/6	Swelling with lids about half-closed	1/6	Swelling with partial eversion of lids
	4/6	Swelling with lids half-closed or greater	2/6	Swelling with lids about half-closed
			3/6	Swelling with lids half-closed or greater

*Dose = 100 mg instilled in one eye.

Table 26. Mortality Produced in Rats by Three-Hour Exposure to Aerosolized Benzotriazole (Sherwin-Williams Company, 1976)

Exposure Concentration mg/l	Percent Mortality
0.78	0
1.46	10
2.03	20
2.23	50
2.71	100

All deaths, except one, occurred during the exposure period; usually during the final half hour. Those animals which survived the treatment appeared normal within two or three days. The only sign of intoxication noted was deep abdominal breathing and open mouth gasping in the rats exposed to the two highest concentrations. Weight gain was not adversely affected in surviving animals throughout the 14-day observation period.

Rats which died from exposure to the benzotriazole aerosol revealed two consistent gross pathological changes upon autopsy. First, the trachea contained a severe accumulation of white frothy fluid; and second, the lungs revealed a moderate to severe incidence of dark red hemorrhagic areas in all lobes. Pulmonary edema was absent.

When the data contained in Table 26 were analyzed by the method of Litchfield and Wilcoxon (1949), the three-hour LC_{50} was found to be 1.91 mg/l with 95% confidence limits of 1.59 to 2.29 mg/l. According to the standards of the Federal Hazardous Substances Act (Federal Register, August 12, 1961), a substance producing an LC_{50} of 2.0 mg/l during an exposure of one hour or less would be considered highly toxic. In this case, however, the exposure period was three hours and it appeared that death may have been due to local respiratory damage rather than absorption and systemic poisoning. Nevertheless, the margin of safety between a no-effect dose and the LC_{100} is quite small for benzotriazole and indicates that exposure to the chemical in air may be extremely hazardous. In situations outside the workroom environment, it is unlikely that such exposures to benzotriazole dust would occur.

The inhalation toxicity of Tinuvin-P was evaluated in studies reported by Ciba-Geigy Corp. (1976). Male and female rats (five of each sex) were exposed to Tinuvin-P dust at 163 mg/l in air for 1.2 hours. No deaths occurred from this treatment, and autopsies performed after 14 days revealed no specific response to the exposure.

d. Subacute Toxicity

The importance of subacute and chronic toxicity studies in defining the deleterious effects of a chemical substance is exemplified by the fact that many humans are exposed to low levels of environmental contaminants throughout their lifetimes. Furthermore, it has become apparent that single-dose (acute) exposure to a chemical often does not affect the same target organs as those following repeated exposures. The additional factors of cumulative effects on metabolic function and other physiological variables, including growth, nutrition, reproduction, and tumor formation, make long-term studies essential in discovering all adverse host-chemical interactions.

Only very limited subacute toxicity data are available concerning the benzotriazole derivatives. These studies were conducted with Tinuvin-P and Tinuvin-327. Ciba-Geigy Corp. (1976) reported that two groups of five male and five female rats were treated by stomach tube with either 1250 mg/kg or 2500 mg/kg of Tinuvin-P suspended in gum arabic. The compound was administered six days each week for a total of four weeks. No deaths resulted from the treatment, and no pathological changes were noted upon autopsy. The same protocol was followed with Tinuvin-327 and produced the same results as for Tinuvin-P.

In addition to the oral toxicity studies, Tinuvin-327 was tested for subacute dermal toxicity (Ciba-Geigy Corp., 1976). Five male and five female rats received 0.4 cc of a 5% suspension of the chemical in gum arabic applied to the shaved skin of the back. Treatment was made six days per week for four weeks. At the end of the study, no deaths had been produced and no local irritation or systemic toxicity was observed.

Tinuvin-P was evaluated for subacute dermal toxicity in both rats and mice (Ciba-Geigy Corp., 1976). The material was applied to the shaved backs of five males and five females of each species for five consecutive days. The compound was applied as a 5% suspension in gum arabic at a dose of 0.1 cc per day for mice and 0.4 cc per day for rats. After eight days of observation, no deaths or other signs of toxicity were observed in any of the treated animals.

Two studies have been conducted in which Tinuvin-P was incorporated into the diet of dogs and rats (Ciba-Geigy Corp., 1976). Forty young male and female rats were exposed to the compound at levels of 0, 0.2, 1.0, and 5.0% in the diet for 14 weeks. The so-called "no-effect" level of treatment was found to be the 0.2% dose, and suggests that Tinuvin-P may produce severe chronic effects.

When tested in three groups of eight beagle dogs at dietary levels of 1,000, 2,000, and 10,000 ppm for 90 days, Tinuvin-P caused no mortality.

However, liver weights were elevated in all treatment groups, and two animals in the 10,000 ppm group displayed toxic symptoms. These results are consistent with those obtained from the subacute treatment of rats and indicate that long-term exposure to Tinuvin-P may cause metabolic alterations of organ function, particularly in the liver.

e. Sensitization

The ability of the benzotriazole derivatives to produce contact sensitization of the skin or other delayed hypersensitivity reactions is apparently very slight. Eastman Kodak Company (1975) has reported that 5-methyl-1H-benzotriazole failed to sensitize any of five guinea pigs. When benzotriazole was tested in guinea pigs, a definite sensitization reaction was not produced.

Studies in humans (see Section III-B-1) have indicated that neither Tinuvin-P nor Tinuvin-327 caused contact skin sensitization by repeated patch testing (Ciba-Geigy Corp., 1976).

f. Teratogenicity

The structural relationship of benzotriazole derivatives to the naturally occurring purines, adenine and guanine, has prompted investigations to determine their ability to produce biochemical interference in cellular processes. It has been suggested that disruption of nucleic acid metabolism by the benzotriazole derivatives may ultimately inhibit cell division and growth.

Early studies by Liedke and coworkers (1954) demonstrated that several substituted benzotriazoles could severely inhibit the development of frog embryos. Developing eggs of the frog *Rana pipiens* were selected for testing at various stages of development: two-cell (stage 3), blastula (stage 8), gastrula (stage 11), and neurula (stage 14). The results of exposing embryos at developmental stage 3 to several benzotriazole derivatives are presented in Table 27. It is apparent from the data presented that derivative 1 produced an almost immediate arrest of growth whereas compounds 2 and 3 did not arrest development until the blastula stage was reached. The authors suggested that compounds which inhibit growth at early stages of development (stage 3) may interfere with enzyme systems involved in cell division. Arrest at later stages (gastrula and neurula) would indicate interference with the process of differentiation.

Table 27. Arrest of Rana pipiens Embryos Upon Continuous Exposure from Stage 3 (Liedke et al., 1954)

Number	Compound	Conc. mg/100 ml	Arrested Stage
1	5-Nitro-benzotriazole	20	3-4
2	4-Methoxy-6-nitrobenzotriazole	20	7-8
3	4-Hydroxy-6-nitrobenzotriazole	20	7-8

Continuous exposures to other benzotriazole derivatives commencing at various stages of differentiation were also evaluated for their effect on embryo development. The results, summarized in Table 28, indicate that compounds 2 and 3, which were not inhibitory at the two-cell stage, inhibited the neurula very strongly. Compound 2 prevented neurulation in concentrations as low as 1.0 mg/100 ml. At concentrations of 0.5 mg/100 ml neurulation was arrested in 50% of the embryos treated at stage 8. Embryos which were not arrested at neurulation progressed only to the tailbud stage (stage 18), whereupon edematous blisters developed followed by the onset of cytolysis as manifested by the loss of yolk and cell granules.

Table 28. Arrest of *Rana pipiens* Embryos Upon Continuous Exposure to Benzotriazole Derivatives (Liedke *et al.*, 1954)

Number	Compound	Conc. mg/100 ml	Exposure Commencing at Stage			
			3	8	11	14
1	5-Nitro-benzotriazole	20	3-4	8	11	14-15
2	5-Nitro-7-methoxybenzotriazole	20, 10, 5	7-8	10-11	12-13	14
	5-Nitro-7-methoxybenzotriazole	2.5, 1	10-11	12-14	12-15	14-15
	5-Nitro-7-methoxybenzotriazole	0.5	--	14, 18	—	--
3	5-Nitro-7-hydroxybenzotriazole	20	7-8	10-11	12	14
	5-Nitro-7-hydroxybenzotriazole	10	10-12	12	13-14	—
	5-Nitro-7-hydroxybenzotriazole	5	11-12	12-14	12-15	18-19
	5-Nitro-7-hydroxybenzotriazole	2.5	--	14-19	—	--

All of the compounds caused severe arrests in the gastrula and yolk-plug stages (stages 11-12) which caused the ectoderm of the blastocoel roof to become indented or bulged, and later collapsed and wrinkled. These substances also produced swollen arrested neurula stages and cytolysis starting at the anterior neural folds.

A subsequent study was undertaken by Liedke and coworkers (1955) in which *Rana pipiens* embryos were treated in the tailbud stage with 4-methoxy-6-nitrobenzotriazole (MNB). Their results indicated that susceptibility to MNB exposure increased with the age of the embryo. When embryos were exposed at stage 8 (blastula), development was slowed but not arrested. Embryos at the tailbud stage, however, were immediately arrested and remained in the same state even after removal from MNB exposure. Table 29 presents the survival rates of tailbud embryos exposed to various concentrations of MNB. Treatment with MNB produced severe morphologic and histologic effects on the developing embryos. These included destruction of the circulatory system, stunting of growth and differentiation, and abnormal development of the heart, eye, and other structures. The authors suggested a mechanism of toxic action that would be consistent with an interference of embryonic differentiation rather than with cell division in general. At the biochemical level, it was postulated that MNB might interfere with nucleic acid and protein synthesis by virtue of its structural relationship to the natural purines. Experimental evidence is not available, however, to support this theory.

g. Mutagenicity

A number of investigators have demonstrated that certain purine antagonists are mutagenic in bacterial systems. Evidence is available which indicates that several benzotriazole derivatives not only exert profound effects on bacterial growth (see Section III-B-6), but are also mutagenic to certain bacterial strains. These effects appear to be the result of interference in nucleic acid synthesis.

In an early study conducted by Greer (1958), several benzotriazole derivatives were evaluated for mutagenicity using a purine-dependent mutant strain of Escherichia coli designated Wp^-. Table 30 summarizes the effects of substituted benzotriazoles on the growth of E. coli strain W and its two purine-dependent mutants, and the mutagenic effect of these compounds

Table 29. Comparison of Survival of *Rana pipiens* Embryos Exposed at Tailbud Stage 17/18 to 4-Methoxy-6-nitrobenzotriazole (Liedke *et al.*, 1955)

Compound	Conc. mg/ml	Hours Exposed	% Survival When Controls Were at Stage:							
			18	19	20	21	22	23	24	25
4-Methoxy-6-nitrobenzotriazole	0.1	10-14	100	100	100	100	100	97	91	58
	0.1	20	100	0[1]						
	0.05	18-20	100	94	94	91	77	77	77	73
	0.05	24	100	30	0					
	0.025	20-44	100	100	100	100	100	100	100	100
	0.025	72	100	100	83	83	35	0		
	0.01	96	100	100	100	90	75	40	0	

---

[1] Single embryos kept in individual dishes sometimes showed 30-50% survival in spite of extreme developmental arrest.

Table 30. The Effects of Substituted Benzotriazoles on the Growth of Escherichia coli Strain W and Two of Its Purine-Dependent Mutants, Including the Mutagenic Activity at the Guanine-Dependent and Streptomycin-Sensitive Loci of Wp- (Greer, 1958)

Benzotriazoles		Escherichia coli Strain W, Mutant Wp⁻ and Mutant Wah⁻*	Effect on Survival and Mutation of Mutant Wp⁻			
		Concentration of Compound 200 μg/ml		% Inhibition of Visible Colony Formation	Mean Factor of Increase Over Spontaneous Mutant-Frequency	
Substitution in Position		Degree of Inhibition†	Concentration (μg/ml)		Purine⁻ to Purine⁺	Streptomycin^s to Streptomycin^r
4	6					
OH	NH_2	—	---	---	---	---
OCH_3	NH_2	+ + +	---	---	---	---
—	NO_2	+ + + +	200	99·9	7	18
OH	NO_2	+ + + +	---	---	---	---
OCH_3	NO_2	+ + +	200	60	8	6

*Wp⁻: requiring guanine, adenine, hypoxanthine, xanthine, or 4-amino, 5-imidazolecarboxamide;
Wah⁻: requiring adenine or hypoxanthine.

† —, no inhibition; + + +, time to reach stationary phase = >2 x control; + + + +, time to reach stationary phase = >2.5 x control.

at the guanine-dependent and streptomycin-sensitive loci of mutant Wp^-. The growth of E. coli in these determinations was limited to one-half maximal by adding guanine, adenine, or glucose as the limiting growth factor for strains Wp^-, Wah^-, and wild-type W, respectively. Mutagenesis was produced by two of the benzotriazole derivatives which were also shown to be strong growth inhibitors.

Although 4-hydroxy-6-nitrobenzotriazole was a strong growth inhibitor of E. coli strains, it did not produce spontaneous mutations. It was subsequently found, however, that the compound significantly depressed induced mutagenesis by 4-nitro-6-hydroxybenzimidazole (Table 31). This effect was not thought to result by growth inhibition alone, but rather may have resulted from replacement of 4-nitro-6-hydroxybenzimidazole by 4-hydroxy-6-nitrobenzotriazole within the cell.

Mutagenicity data are particularly important, not only for the assessment of potential genetic harm, but also in predicting carcinogenicity. It is widely recognized that carcinogenic chemicals are almost always potential mutagens as well (Miller and Miller, 1975). The International Agency for Research on Cancer now includes mutagenicity data in its monographs on the evaluation of carcinogenic risk of chemicals to man (Loprieno, 1975). However, since the demonstration of mutagenicity does not establish carcinogenicity, the data presented above must be regarded as suggestive of the need for further research in higher organisms. Also, the more commercially important benzotriazoles should be tested first in mutagenicity screening systems.

h. Carcinogenicity

There is no direct evidence yet available to indicate whether benzotriazole or its derivatives may present a carcinogenic threat to

Table 31. The Antimutagenic Effect of 4-OH-6-NO_2-Benzotriazole on Mutagenesis in Escherichia coli Wp⁻ Induced by 4-NO_2-6-OH-Benzimidazole (NHB) (Greer, 1958)

		None			[illegible]		
Marker	[illegible]	Spont. m.f.† (a)	196 µM (35 µg/ml) NHB induced m.f.† (b)	Mean factor of increase (b/a)	NHB m.f.†	196 µM NHB m.f.† (d)	Mean factor of decrease (b/d)
Purine [illegible]	Zero After [illegible]	[illegible] [illegible]	953 4180	103 320	25 7.0	173 975	5.5 6.3
Streptomycin [illegible]	Zero After [illegible]	[illegible] [illegible]	137 285	550 203	0.25 4.7	14.8 32.4	9.2 [illegible]

*Antagonist was added to growing [illegible] cultures 3 hours before addition of NHB.
†m.f. = mean mutant frequency [illegible]

man. It may only be suggested that because of its potential effects on nucleic acid metabolism and its actions on the growth of bacterial (see Section III-B-6) and animal cells (see Section III-B-7) benzotriazole can be suspect as a tumorigenic agent.

In a report abstracted from the Russian literature (Vasil'eva, 1970) it was disclosed that benzotriazole was probably not carcinogenic for rats, but might induce leukemia in hybrid mice. Benzotriazole was administered orally once weekly for 46 weeks at 100 mg/kg body weight to a group of 315 male and female (C57 x CBA) F1 mice (weight 18 to 20 grams). The same dosage schedule was used to treat 272 male and female Wistar and non-inbred rats by subcutaneous injection. Rats received total doses of 900-1000 mg while mice received a total of 92 mg.

Three rats developed tumors: one pulmonary fibroma, one mammary adenoma, and one mesenteric polymorphocellular sarcoma. In addition, benzotriazole induced an adipose dystrophy of the liver with necrotic foci.

In mice, the results were difficult to interpret due to the high (55.9%) incidence of tumors in untreated controls (8.5% had malignant tumors and 3.4% had leukemia). Among the benzotriazole-treated mice, the incidence of leukemia was 13.7%, which was significantly higher than controls. However, mice treated by injection with the drug vehicle alone also developed leukemia in 11.1% of the group. Therefore, the observed incidence of leukemia in the benzotriazole-treated mice may have been due, at least in part, to the effect of the chemical solvent.

Extensive carcinogenesis testing with benzotriazole is presently in progress at the National Cancer Institute (Weisburger, 1976).

This work is scheduled to be completed by October, 1976, and should clarify the observations as reported in the above study.

i. Behavioral Effects

No attempts have been made to determine whether exposure to the benzotriazole derivatives can alter patterns of behavior. It might be predicted, however, that, because of its demonstrated effects on central nervous system function, benzotriazole compounds may induce centrally-mediated behavioral changes. On the other hand, the high dosage level which would probably be required to act upon the brain essentially precludes the possibility of such an event occurring at predicted environmental levels.

j. Possible Synergisms

The environmental exposure to chemical contaminants rarely occurs as a contact with a single pure substance. Nevertheless, it is generally very difficult to obtain data concerning the synergistic toxicity of chemicals either in the workplace or in the environment.

A single report has been encountered which presented the effects of feeding benzotriazole or 5-methylbenzotriazole on the incidence of liver tumors in rats produced by 3'-methyl-4-dimethylaminoazobenzene (Clayton and Abbott, 1958). The benzotriazoles were added to the diet at a 0.5% level and fed for eight weeks along with the carcinogen at a level of 0.064%. The results, as summarized in Table 32, demonstrate that neither of the benzotriazoles significantly affected tumor incidence when compared to positive controls. Furthermore, the chronic feeding of the two benzotriazole compounds did not produce any mortality among treated animals.

Table 32. The Effect of Benzotriazole and 5-Methylbenzotriazole on the Incidence of Liver Tumors in Male Rats Produced by Feeding 3'-Methyl-4-dimethylaminoazobenzene (Clayton and Abbott, 1958)

3'-Me-DAB* (weeks fed)	Basal (weeks fed)	Other Additions			Survival† (16 weeks)	Tumors‡ (percent)
		Compound	Amount	Weeks Fed		
1-8	9-16	None			24/25	96
1-8	9-16	Benzotriazole	0.5%	1-8	25/25	72
1-8	9-16	5-Methylbenzotriazole	0.5%	1-8	25/25	80

*3'-Me-DAB = 3'-methyl-4-dimethylaminoazobenzene.

†Survival = number of [illegible] experiment over number at start.

‡Percent of survivors that had liver tumors.

3. Effects on Other Vertebrates

a. Toxicity to Fish

(1) Benzotriazole

The effects of benzotriazole on several species of fingerling fish were determined in studies conducted by the Sherwin-Williams Company (1975). Trout, bluegills, and fathead minnows were treated in static and dynamic test systems with mortality measurements being made after 48 and 96 hours of continuous exposure. Trout were tested under dynamic conditions only.

Table 33 presents the survival at various concentrations for bluegills and minnows under static and dynamic conditions. The median tolerance limit (TL_m) values (concentration required to produce death in 50% of the test animals) were found to be 27.5 ppm after 48 hours and 25 ppm after 96 hours in the static system. Under dynamic conditions, the TL_m values were 30.2 ppm after 48 hours and 28 ppm after 96 hours. The results indicated that no significant differences in toxicity could be attributed to static versus dynamic exposure. However, in both systems mortality was higher after 96 hours than after 48 hours. These findings would suggest a possible cumulative toxic effect in fish.

The results of treating fingerling trout with benzotriazole under dynamic test conditions are presented in Table 34. The calculated TL_m values were 15 and 12 ppm at 48 and 96 hours, respectively. These data indicate that trout are about twice as sensitive to benzotriazole as bluegills and fathead minnows. Furthermore, it can be seen from the table that mortality among trout was considerably higher after 96 hours than after 48 hours, and again suggests a possible cumulative toxic effect.

Table 33. Static and Dynamic Exposure of Bluegills and Fathead Minnows to Benzotriazole (Sherwin-Williams Co., 1975)

	STATIC			DYNAMIC		
		% Mortality			% Mortality	
Concentration (ppm)	No. Fish	48 hour	96 hour	No. Fish	48 hour	96 hour
22	15	0	0	—	—	—
24	15	13.3	46.7	—	—	—
26	15	26.7	60.0	15	20	35
28	15	60.0	86.7	15	32	50
30	—	—	—	15	41.9	66.1
32	—	—	—	15	52.3	80
34	—	—	—	15	63.0	95.2
Control	15	0	0	15	0	0

Table 34. Dynamic Exposure of Fingerling Trout to Benzotriazole (Sherwin-Williams Company, 1975)

Concentration (ppm)	No. Fish	% Mortality 48 hour	% Mortality 96 hour
10	30	3.3	3.3
12	30	25.0	30.0
14	30	41.6	90.0
16	30	55.0	100.0
Control	30	0	0

(ii) Tolyltriazole

The acute toxicity of tolyltriazole to the fathead minnow has been determined using a static test system (Sherwin-Williams Company, 1975). The protocol employed in the test was that issued by the Pesticides Regulation Division of the Environmental Protection Agency (January 20, 1971). For the sake of comparison, the acute toxicity of 74% p, p'DDT was evaluated under the same conditions as for tolyltriazole. Following a preliminary screening study, 20 fish were treated at each of four tolyltriazole concentrations: 35.50 ppm, 28.20 ppm, 22.40 ppm, and 17.80 ppm. The resulting LC (lethal concentration) values, as calculated by the method of Litchfield and Wilcoxon (1949), are presented in Table 35. It is apparent that tolyltriazole has a similar toxic potency to benzotriazole, and also may produce cumulative toxic effects. Clearly, however, p, p'DDT is far more toxic to the fathead minnow than is either of the benzotriazoles tested.

b. Toxicity to Amphibians

Several benzotriazole derivatives having close structural similarity to naturally occurring purines were shown to inhibit the development

Table 35. LC Values (ppm) and Their Confidence Limits (at p = .05) in Fathead Minnows (Sherwin-Williams Co., 1975)

	74% p, p'DDT			Tolyltriazole		
	24 hour	48 hour	96 hour	24 hour	48 hour	96 hour
LC_1	0.0460	0.0485	0.0360	23.00	14.00	14.20
Lower Limit	0.0438	0.0462	0.0343	19.16	13.33	13.52
Upper Limit	0.0480	0.0509	0.0378	27.60	14.70	14.91
LC_{50}	0.1180	0.1010	0.0945	36.90	29.80	25.50
Lower Limit	0.1124	0.0962	0.0900	30.75	28.38	24.29
Upper Limit	0.1239	0.1061	0.0992	44.28	31.29	26.78
LC_{99}	0.3010	0.2110	0.2980	68.50	62.50	46.00
Lower Limit	0.2867	0.2010	0.2838	57.08	59.52	43.81
Upper Limit	0.3161	0.2216	0.3129	82.20	65.63	48.30
Slope	1.49	1.37	1.51	1.14	1.38	1.28

of the *Rana pipiens* frog embryo (Liedke *et al.*, 1954, 1955). These studies are discussed in Section III-B-2-f of this report.

4. Effects on Invertebrates

A search of the published literature has not revealed any reports concerned with the effects on invertebrates of benzotriazole and its derivatives.

5. Effects on Plants

Several reports have indicated that benzotriazole can produce distinct morphological changes in a variety of plants. In an early study by Davis (1954) benzotriazole was shown to cause profound changes in the tomato plant. These changes were characterized by a breaking of apical dominance, reduced number of leaflets per leaf, elimination of leaf serrations, cupping of the leaflets, and elongated petioles which were unable to support the weight of their own leaves. These formative effects were produced only by exposure of the tomato plant roots to benzotriazole; application to the foliage in concentrations as high as 1000 pppm had no effect. When 50 ml of a 50 ppm benzotriazole solution was applied daily for ten days to the sand surrounding tomato plant roots, formative effects were noted within two to three weeks following the final application.

Davis (1954) suggested that benzotriazole may be a competitive antagonist of the important biological molecules, indole, and the purine bases. However, the effects of benzotriazole could not be reversed by daily applications of 50 ml of either 0.5 to 50 ppm of indoleacetic acid or 250 ppm adenine sulfate. The formative effect of benzotriazole on tomato plants could be duplicated by benzothiazole but not by indole, benzimidazole, benzoxazole, benzothiophene, benzothiadiazole, thiophene, pyrolle, thiazole, imidazole, or 1,2,4-triazole.

The action of benzotriazole on several plant species was later investigated by Klingensmith (1961). The procedures employed were: (1) root growth tests in cucumber and barley seedlings, (2) gross morphological studies in tomato, bean, coleus, soybean, and wheat, and (3) tissue culture studies using tobacco stem segments.

Benzotriazole and 5-chlorobenzotriazole were evaluated for repression of root elongation in cucumber seedlings. A substituted purine, 6-methylmercaptopurine, was also included for comparison purposes. The concentration of each compound required to produce 50% repression of root elongation is presented in Table 36.

Table 36. Repression of Cucumber Root Elongation. Elongation of Primary Root, 96 Hours at 25°C (Klingensmith, 1961)

Compound	Concentration Causing 50% Repression
Benzotriazole	1×10^{-3} M
5-Chlorobenzotriazole	1×10^{-4} M
6-Methylmercaptopurine	3.5×10^{-4} M

Comparisons were also made of the effects of benzotriazole, benzothiazole, and benzimidazole on the growth of barley roots and cucumber roots. The action of these compounds was measured as the effect upon the conversion of endosperm to dry matter in barley roots (Figure 11) and the repression of cucumber primary root elongation (Figure 11). Although these

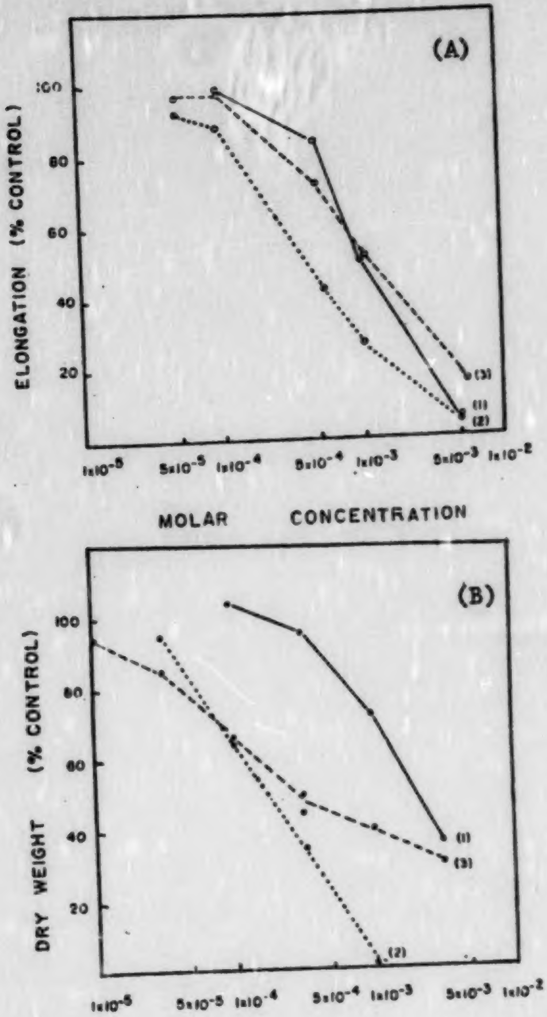


Figure 11. (A) Effect of Certain Benzazoles Upon the Elongation of the Primary Root of Cucumber Seedlings (seedlings grown in presence of the compound at 25°C in darkness for 96 hours); (B) Effect of Certain Benzazoles Upon Dry Weight of Barley Roots (seedlings grown in aerated deep cultures, 25°C, in darkness for 6 days) (Klingensmith, 1961) (1) Benzimidazole, (2) Benzothiazole, (3) Benzotriazole

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compounds were considered to be functional analogs of the purines, the addition of adenine did not reverse the inhibitory effect of the three chemicals on cucumber root elongation. In fact, when combined with benzotriazole, adenine markedly enhanced the inhibition of root growth.

When applied to the soil of existing bushbean plants, benzotriazole produced death at 5×10^{-2} M, and at 1×10^{-2} M there was nearly complete inhibition of internodal elongation with simultaneous thickening of the stem (Klingensmith, 1961). Axillary bud activity was stimulated by the treatment, however. Similarly, treatment of tomato plants at 5×10^{-2} M caused early death, whereas 1×10^{-2} M concentrations caused persistent morphological changes the same as those previously described by Davis (1954). When applied at a concentration of 1×10^{-2} M to the roots of barley, oats, and wheat, benzotriazole increased the production of tillers and shoots. This effect was suggested as being due to repression of internodal elongation. At 1×10^{-2} M, benzotriazole produced a distinct cupping of the leaves in coleus plants. The cupping of all new leaves persisted for 14 weeks after the application of benzotriazole to the root medium.

Because benzotriazole caused a suppression of apical dominance in the plants described above, Klingensmith (1961) suggested that the effect may be correlated with auxin transport in the tissue. When examined in tissue culture with tobacco stem segments, however, benzotriazole did not inhibit the polar transport of auxin. Therefore, the suppression of apical dominance by benzotriazole could not be explained. Furthermore, in light of unsuccessful attempts to reverse root elongation inhibition by the addition of adenine, it appears that benzotriazole did not act as a functional purine antimetabolite in these experiments.

The benzotriazole derivative 5-chlorobenzo-1,2,3-triazole was tested by Schweizer and Rogers (1964) in several plant systems. They found that the chemical inhibited wheat root elongation and growth of carrot explants, produced chlorosis (decreased chlorophyll content), and depressed catalase activity. These results are summarized in Table 37.

Table 37. Physiological Effects on Plants by 5-Chlorobenzo-1,2,3-triazole* (Shweizer and Rogers, 1964)

Compound	Carrot Explant Growth (10^{-3} M)	Wheat Root Elongation (2.5 x 10^{-4} M)	Chlorophyll in Corn (10^{-3} M)		Spinach Catalase Activity (10^{-3} M)
			WF9X M14	38-11	
5-Chlorobenzo-1,2,3-triazole	0.0	41.7	90	88	90

*Data are expressed as percent of controls.

Several alkylbenzotriazoles were studied by Picci and Sparatore (1968) for their effects on the elongation of sections of oat coleoptiles *in vitro*. They found that at low concentrations the compounds, including unsubstituted benzotriazole, were stimulatory to growth, while at higher concentrations (10^{-3} M) almost all were growth inhibitors (Table 38).

6. Effects on Microorganisms

a. Effects on Bacteria

Benzotriazole and many of its derivatives exert profound effects on the growth and survival of numerous types of bacteria. These effects

Table 38. Effect of Alkylbenzotriazoles on the Growth of Oat Coleoptile Segments *In Vitro**
(Picci and Sparatore, 1968)

Substance	Molar Concentration				
	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}
Benzotriazole (1H $\rightleftarrows$ 2H)	-25	40	50	90	135
1-Methylbenzotriazole	-25	35	75	115	150
1-Ethylbenzotriazole	10	20	40	75	50
1-Propylbenzotriazole	-45	-20	5	60	50
1-Butylbenzotriazole	-80	-35	0	15	-20
2-Methylbenzotriazole	-5	20	55	65	60
2-Ethylbenzotriazole	-60	0	40	60	55
2-Propylbenzotriazole	-55	-40	15	40	30
2-Butylbenzotriazole	-15	35	75	85	65

*Data expressed as percent increase or decrease over controls.

seem, for the most part, to be related to the ability of benzotriazole derivatives to act as purine antagonists and thereby disrupt vital metabolic processes.

The ability of benzotriazole to act as a potential antipurine on a purine-requiring strain of *E. coli* was investigated by Collier and Huskinson (1957). A strain of *E. coli* had been developed for these studies which required the presence of adenine, guanine, hypoxanthine, or xanthine for satisfactory growth. This strain was used as a means of detecting antipurine activity by chemicals which inhibited the growth of the bacteria in the presence of added purines. The purine requirement for growth in the *E. coli* strain is illustrated in Figure 12.

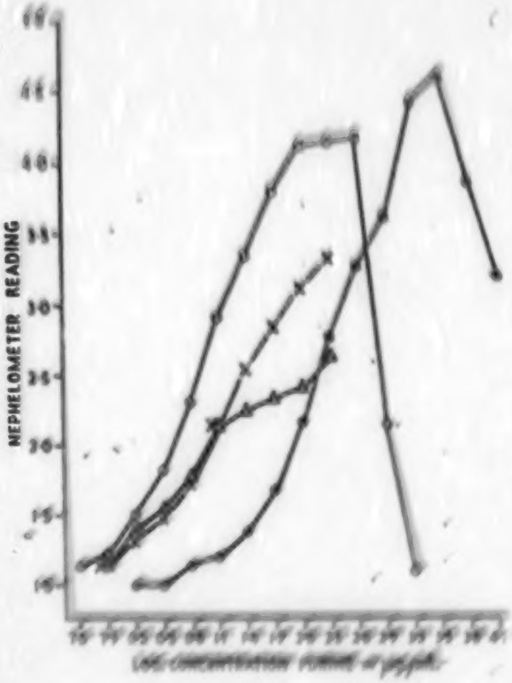

Figure 12. Growth of *Escherichia coli* [illegible] in Response to Addition of Purines to the Culture Medium (Collier and Huskinson, 1957)
●———●: hypoxanthine; O———O: adenine; X———X: guanine
Δ———Δ: xanthine

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The addition of benzotriazole to culture media containing serially increasing concentrations of guanine shifted the growth curve as pictured in Figure 13. While low concentrations of benzotriazole stimulated bacterial growth, higher concentrations were inhibitory. Since stimulation was absent from the lower part of the curve, it was suggested that benzotriazole cannot replace purines for E. coli. In actively dividing cells, however, it appeared possible that benzotriazole might be more efficiently utilized than purines to form some essential metabolic product. Benzotriazole was not able to support growth of the purine-requiring E. coli strain in the absence of adenine or guanine.

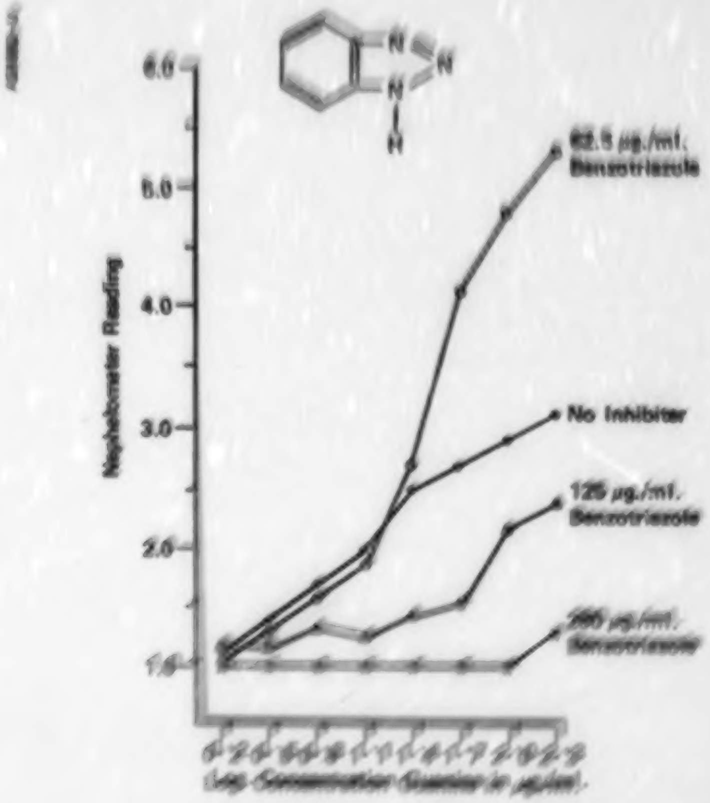

Figure 13. Effect of Benzotriazole on the Growth of Escherichia coli 8242 in Presence of Guanine (Collier and Huskinson, 1957)

The authors also found that the addition of 250 μg/ml phenol to the test medium doubled growth in the presence of 200 μg/ml guanine. When benzotriazole was added to this system, growth inhibition was evident at all benzotriazole concentrations, as manifested by a horizontal shift of the log purine-growth curve. It was noted that a vertical depression of the growth curve, as in Figure 13, characterizes inhibition which is non-competitive, whereas a horizontal shift is typical of competition resulting in an increased requirement for purine.

As part of a screening program for potential anticancer agents, benzotriazole was evaluated for its effect on the growth of several bacterial systems (Foley et al., 1958). These results are presented in Table 39.

Somewhat different results were obtained by the Sherwin-Williams Company (1976) when they studied the effects of low-level benzotriazole exposure on wastewater microorganisms. These investigators incubated a seed (5 ml per liter of dilution water) prepared from the supernatant of settled domestic sewage in a waterbath at 20°C for five days with varying concentrations of benzotriazole. The resultant effects on bacterial growth, as outlined in Table 40, seem to indicate that benzotriazole may act as a growth promoter at the concentrations tested.

Table 40. Effect of Benzotriazole on the Growth of Microorganisms from Wastewater (Sherwin-Williams Company, 1976)

Benzotriazole Added (mg/L dilution water)	Total Colony Count (per ml)
0 initial	56,000
0 5 day	151,000
0.66 5 day	207,000
3.3 5 day	217,000
6.6 5 day	183,000
13.2 5 day	164,000

Table 38. Bioassay of Benzotriazole Using Various Microbiological Systems (Foley *et al.*, 1958)

Bioassay Microorganism	Incubation Hour	 °C	Test Vol. (ml)	Assay Medium	ID_{50}* (gm/ml)
Streptococcus fecali	24	37	10	Folic acid	$>10^{-3}$
Lactobacillus casei	48	37	10	Riboflavin	$10^{-3} - 10^{-4}$
Escherichia coli	48	37	10	Inorganic salts, glucose	$10^{-3} - 10^{-4}$
Lactobacillus arabinosus	48	37	10	Nicotinic acid	$>10^{-3}$
Lactobacillus arabinosus	48	37	10	Pantothenic acid	$>10^{-3}$
Leuconostoc citrovorum	48	37	10	Citrovorum factor	$>10^{-3}$
Lactobacillus fermenti	48	37	10	Thiamine	$10^{-3} - 10^{-4}$
Candida albicans	48	37	10	Inorganic salts, glucose	$10^{-3} - 10^{-4}$
Saccharomyces carlsbergensis	22	30	6	Pantothenic acid plus pantothenate	$10^{-3} - 10^{-4}$
Streptococcus fecalis	14	37	6	Hydrolyzed casein, glucose, salts, vitamins	$10^{-3} - 10^{-4}$
Lactobacillus casei	22	37	6	Hydrolyzed casein, glucose, salts, vitamins	$>10^{-3}$
Escherichia coli	17	37	6	Inorganic salts, glucose	$10^{-3} - 10^{-4}$
Tetrahymena pyriformis	96	25	4	Amino acids, glucose, salts, vitamins	$10^{-3} - 10^{-4}$
Glaucoma scintillans	96	25	4	Casein, amino acids, vitamins, salts	$10^{-3} - 10^{-4}$
Colpidium campylum	96	25	4	Casein, amino acids, vitamins, salts	$10^{-3} - 10^{-4}$
Neurospora crassa	48	32	20	Salts, sucrose, biotin	$10^{-3} - 10^{-4}$

*ID_{50} = Concentration causing 50% growth inhibition.

These results should be compared with those obtained by Foley *et al.* (1958; Table 39) with regard to the fact that benzotriazole levels were much lower in this study, and that the wastewater sample contained an undefined mixture of microorganisms.

Tolyltriazole was incubated with wastewater microorganisms under similar BOD test conditions as for benzotriazole (Sherwin-Williams Co., 1976). The results, presented in Table 41, indicate that slight reduction in colony populations occurred with tolyltriazole treatment.

Table 41. Effect of Tolyltriazole on Biochemical Oxygen Demand and Growth of Wastewater Microorganisms (Sherwin-Williams Co., 1976)

Sample Concentration (mg/L)	BOD (mg/L)	Surviving Colonies per ml BOD Test Solution
Dilution Water (control)	0.67	601,000
Seeded Dilution Water (control)	0.73	318,000
Tolyltriazole 0.2	0.39	234,000
Tolyltriazole 2.0	0.45	441,000
Tolyltriazole 20.0	1.12	125,000

It was concluded that, at the concentrations tested, tolyltriazole was not significantly toxic to the wastewater bacteria. However, it appears that at levels in excess of 20 mg/L tolyltriazole may significantly increase toxicity and demand for oxygen.

b. Effects on Viruses

Several derivatives of benzotriazole have been shown to possess very high virus inhibitory activity. Testing was conducted by Tamm and coworkers (1961) using both influenza B virus in the chorioallantoic membrane *in vitro* and poliovirus type 2 in monkey kidney cell cultures. These results are presented in Tables 42 and 43.

The data in Table 42 show that benzotriazole was only one-half as active as benzimidazole. However, increasing chloro substitution in the benzene-ring portion of the molecule caused considerably enhanced activity. The substitution of fluorine for chlorine in the structure was not as effective in inhibiting viral multiplication.

Table 42. Effect of Benzotriazole and Derivatives on the Multiplication of Influenza B Virus in Chorioallantoic Membrane* (Tamm et al., 1961)

Benzotriazole Derivative	75% Virus Inhibitory Concentration (VIC)[a] (μM)	Relative Inhibitory Activity (RIA)[b]
Benzotriazole	7,500	0.47
5-Chloro	610	5.7
5,6-Dichloro	54	65
4,5,6-Trichloro	12	290
4,5,6,7-Tetrachloro	3	1,200
5-Fluoro	2,600	1.3
5-Trifluoromethyl	180	19
5,6-Dimethyl	>5,300	<0.66

*Infected chorioallantoic membrane cultures were incubated at 35°C for 41 hours and influenza virus was measured in the supernatant by the hemagglutination technique.

[a] Concentration (μM) required to cause 75% reduction in yield of influenza virus.

[b] Relative to benzimidazole.

When tested against poliovirus type 2 in monkey kidney cell cultures, benzotriazole was equal in activity to benzimidazole (Table 43). Benzotriazole was significantly more effective against poliovirus than influenza, whereas the reverse was true for the tri- and tetrachloro derivatives. Similar to the previous observation with influenza virus, benzotriazole derivatives became progressively more active as chlorine substitution in the benzene ring increased.

Table 43. Effect of Benzotriazole and Derivatives on the Multiplication of Poliovirus Type 2 in Monkey Kidney Cells _In_ _Vitro_* (Tamm _et_ _al_., 1961)

Compound	75% Virus Inhibitory Concentration (VIC) (μM)	Relative Inhibitory Activity (RIA)[b]
Benzimidazole Derivative		
Benzimidazole	2,800	1
Benzotriazole	2,800	1
5-Chloro	500	5.6
5,6-Dichloro	73	38
4,5,6-Trichloro	23	120
4,5,6,7-Tetrachloro	8.1	350
5-Trifluoromethyl	240	12

*Infected monkey kidney cell cultures were incubated at 36°C for 48 hours and poliovirus was measured in the supernatant by infectivity titrations.

[a] Concentration (μM) required to cause 75% reduction in yield of poliovirus.

[b] Relative to benzimidazole.

During the entire course of their investigations, Tamm and coworkers (1961) evaluated a total of 65 benzimidazole and benzotriazole derivatives against influenza virus and 25 derivatives against poliovirus. In both test systems, tetrachlorobenzotriazole was the most potent antiviral compound tested. However, the mechanism of action for this antiviral effect was not established.

c. Effects on Yeast

In experiments conducted by Loveless _et al_. (1954) it was established that benzotriazole was inhibitory to the growth of yeast (_Saccharomyces cerevisiae_) at 1 gram/ml but did not affect cell division. In subsequent studies with the yeast _Candida albicans_ (Bianchi, 1961), it was shown that benzotriazole and chlorobenzotriazole at molar concentrations of 10^{-2} to 10^{-4} increased the growth rate and phenotype of small-type colony variants. This alteration in growth was temporary only, and colonies reverted to the small-type when transferred to plates of complete media. These observations suggested an effect on a metabolic process such as nucleic acid metabolism, which occurred only in the continued presence of the chemical.

7. _In Vitro_ and Biochemical Studies

Several studies have been conducted with benzotriazole and its derivatives to determine their effects on cultured cells, isolated mitochondria, and certain isolated enzymes. These investigations have confirmed the susceptibility of certain cells and metabolic processes to disruption by the benzotriazoles.

a. Effects on Isolated Organs

A search of the published literature has not identified any reports on the effect of benzotriazole or its derivatives on isolated or prefused organs.

b. Effects on Cell Cultures

The use of cytotoxicity testing in cell cultures has been used as a primary screen for the detection of potential antitumor agents. Benzotriazole has been tested in tissue culture systems as part of a screening program. Smith _et al_. (1959) reported the cytotoxicity of benzotriazole to cultured KB cells, derived from a human nasopharyngeal epidermoid carcinoma. They found the ID_{50} (concentration that caused 50% inhibition of growth) to be 150 μg/ml (range = 120 to 190 μg/ml). Eagle and Foley (1958) found the ID_{50} for benzotriazole when incubated with cells isolated from normal adult human liver to be in the area of 100 μg/ml. It should be noted that traditional purine analogs (e.g., 8-azaguanine, 6-mercaptopurine) were far more toxic to cells in culture than was benzotriazole. However, Smith _et al_. (1963) demonstrated that toxicity in whole animals could not be closely predicted from cytotoxicity data using KB cells.

A number of benzotriazole derivatives were evaluated for cytotoxicity in a tissue culture system employing monkey kidney cells (Tamm _et al_., 1961). The investigators determined the molar concentrations of each compound required to cause microscopic cell damage. Compound-induced cell injury was ranked on a scale of 1+ (slight) to 4+ (severe). Figure 14 compares the concentration-time dependency of damage produced by various benzotriazoles with monkey kidney cells _in vitro_. It is readily apparent from the individual damage-time curves that increasing chloro substitution of the benzotriazole molecule markedly enhanced its toxic potency on a molar basis.

c. Effects on Isolated Organelles

In studies employing isolated rat-liver mitochondria, it was determined that 4,5,6,7-tetrachlorobenzotriazole was a potent uncoupler of

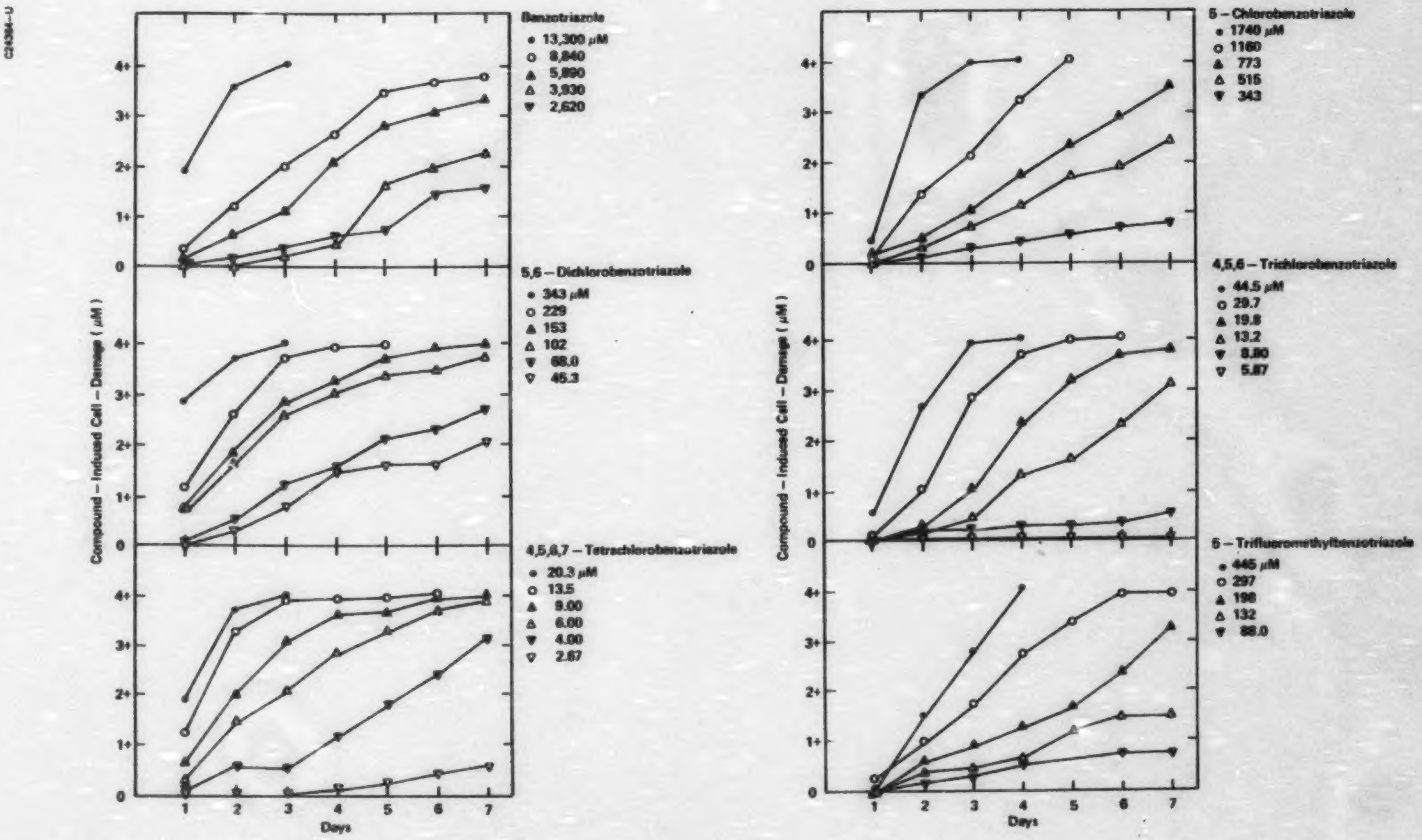

Figure 14. Compound Induced Damage-Time Curves with Selected Benzotriazole Derivatives in Monkey Kidney Cells (Tamm et al., 1961)

oxidative phosphorylation (Parker, 1965; Jones and Watson, 1967). In producing this effect, tetrachlorobenzotriazole had more than eight times the potency of 2,4-dinitrophenol, a classical uncoupling chemical (Jones and Watson, 1967). Other benzotriazole derivatives which were found to uncouple oxidative phosphorylation, but were less active than the tetrachloro derivative, are 5-chloro-4-nitrobenzotriazole and 5-nitrobenzotriazole (Parker, 1965). Data on the activity of unsubstituted benzotriazole as an uncoupler were not available.

d. Effects on Isolated Enzyme Systems

Several in vitro enzymatic systems have been employed for the detection of potential anticancer agents. These assays are designed to identify compounds which might selectively inhibit a system and result in more harm to malignant than normal cells. Benzotriazole was evaluated by Ciaccio et al. (1967) for the inhibition of several enzyme systems. These studies are summarized in Table 44.

Table 44. Effect of Benzotriazole on the Inhibition of Selected Enzymatic Systems In Vitro (Ciaccio et al., 1967)

Enzyme System	Test (Substrate)	Neg. Log Molarity	Percent Inhibition
Dehydrogenase	Lactate Dehydrogenase	2.0	0
	Glycerophosphate	2.0	0
Glycolysis	Glucose	3.0	0
Nucleic Acid Enzyme	Deoxyribose Aldolase	3.0	59
	Deoxyribose Aldolase	3.0	48
	Thymidine Phosphorylase	3.0	0

As indicated in Table 44, benzotriazole was an effective inhibitor of deoxyribose aldolase. This enzyme was suggested as being part of one pathway for the biosynthesis of the deoxyribose portion of DNA. A common purine analog, 8-azaxanthine, was also shown in the same test system to be an inhibitor of deoxyribose aldolase activity (Ciaccio _et al_., 1967). However, it has not been established whether this enzyme inhibitory effect is correlated with any structural similarities to the naturally occurring purines.

IV. Regulations and Standards

A. Current Regulation

A search of the Food Drug Cosmetic Law Reporter (Commerce Clearing House, Inc., Chicago, Illinois) reveals that no regulations currently exist for pesticidal, drug, or food applications of benzotriazole.

Several restrictions have been placed on the use of the benzotriazole-derivative UV-light stabilizers. These limitations are summarized in Table 45.

The transportation of hazardous materials by rail and highway is regulated by the Hazardous Materials Regulation Board of the Department of Transportation. In January, 1974, the Department of Transportation proposed extensive changes in the rules governing the transport of hazardous chemicals, especially by air. These changes, published in the Federal Register (January 24, 1974) listed a large number of chemical substances. However, neither benzotriazole nor its derivatives are included on this list or are classified as being hazardous.

B. Concensus and Similar Standards

Limits have been established for maximum permissible exposure to hazardous chemicals by several agencies. Threshold limit values (TLV's) for chemicals in the workroom environment have been established by the American Conference of Governmental Industrial Hygienists. These TLV's, which are revised and updated each year, do not, however, include benzotriazole or any of its derivatives.

Exposure limits for hazardous substances have also been set by the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health. Their list of standards which has been published in the Federal Register (October 19, 1972) does not include any derivatives of benzotriazole.

Table 45. Food and Drug Administration Status of Ciba-Geigy Stabilizers - July 1973 (Ciba-Geigy, 1976)

I. Existing Approvals

1. TINUVIN P

A. Acrylics, rigid, semirigid and modified (121.2566/121.2591)
max. conc. - no restrictions
max. thickness - no restrictions
food limitations - no restrictions

B. Rigid vinyl and vinyl chloride copolymers (121.2566/121.2521)
max. conc. - 0.25%
max. thickness - no restrictions
food limitations - no restrictions

C. Polystyrene (121.2566/2510)
max. conc. - no restrictions
max. thickness - no restrictions
food limitations - dry foods with the surface having no free fat or oil and

Polystyrene and modified polystyrene containing less than 10% rubber (121.2566/2510)
max. conc. - 0.25%
max. thickness - no restrictions
food limitations - nonalcoholic food only

2. TINUVIN 326

Olefin polymers, including EPDM (121.2566/2501)
max. conc. - 0.5%
max. thickness - no restrictions
food limitations - non-fatty foods, food with less than 8% alcohol

3. TINUVIN 328

Adhesives (121.2520)
max. conc. - no restrictions
max. thickness - no restrictions
food limitations - no restrictions

II. FDA Opinions in Effect

TINUVIN 327 may be used at levels up to 0.5% in polypropylene slit film and related materials in applications involving contact with dry foods containing no free fat or oil.

TECHNICAL SUMMARY

Benzotriazole and its commercially significant derivatives are light colored powders, relatively insoluble in water, and chemically stable under normal conditions of storage and use. They are characterized by generally broad absorption in the 300-400 nm region of the UV spectrum (Dal Monte et al., 1958; Ciba-Geigy Corp., undated).

Commercial production of benzotriazole is via diazotization of o-phenylenediamine with nitrous acid (Levy, 1966; Long, 1971). The total production of benzotriazoles is estimated to be approximately 5-6 million pounds per year in the United States. The majority of this output is used in anticorrosion applications, especially in the protection of copper and copper alloys. Benzotriazole forms a thin, highly stable, transparent monomolecular polymeric film on copper surfaces, consisting mainly of cuprous benzotriazole units (Roberts, 1974; Ogle and Poling, 1975). The film is thermodynamically and chemically quite stable and offers excellent protection from chemical attack under the usual corrosion inducing conditions. One of the major uses of benzotriazole as an anticorrosion agent is in glycol-based antifreezes for automotive applications. It is used also in recirculating water systems such as power plant cooling units, and for the protection of copper alloys in architectural and decorative applications.

Approximately 20-30% of benzotriazoles produced are derivatives which are incorporated into various substrates susceptible to degradation on exposure to light in the 300-400 nm range. These benzotriazole derivatives (various 2-(2'-hydroxyphenyl)-benzotriazoles) are capable of absorbing light and dissipating the energy as heat and molecular vibrations, thereby protecting the substrate

(Ciba-Geigy, undated). Other than under special conditions of intense radiation at short wavelengths in the laboratory, benzotriazole compounds are photochemically stable. Polypropylene is the chief resin that is protected by benzotriazole stabilizers. Other UV protective applications include paint formulations, clear coatings, and oils used as solvents and dispersants for insecticides. In the latter application, the benzotriazole derivative is placed directly into the environment during use.

There are a number of photographic applications for benzotriazole, all of which apparently use very small quantities of the material and are unlikely to result in significant environmental contamination with benzotriazoles.

The photochemical stability of benzotriazoles at wavelengths encountered at the surface of the earth, coupled with the chemical stability of the benzene ring and especially the triazole ring, suggest that benzotriazoles in contact with air, water, or sunlight are likely to be quite stable and persistent. And, in fact, the 2-substituted benzotriazoles have been detected at ppb in river water and ppm in river sediment downstream from a production plant (Jungclaus, 1977). While the biodegradability of benzotriazoles has not been studied specifically, there is some evidence that the flora of wastewater treatment plants will tolerate these compounds in industrial wastewater effluent in concentrations on the order of magnitude of 10 mg/ml (Quinn, 1972, 1973). Also, they will pass through a trickling filter treatment plant (Jungclaus, 1977).

Benzotriazole and its derivatives have not been extensively studied for biological activity, especially in recent years. They are generally considered to be relatively hazard-free materials (Eastman Kodak, 1975). Toxicity testing in humans has been limited mainly to patch tests for allergic sensitization

(Ciba-Geigy, 1976) to 2-(2'-hydroxyphenyl)-benzotriazoles, with negative results. Manufacturers have indicated no experiences with occupational poisoning.

There are no accounts in the literature concerned with absorption or elimination of benzotriazoles in animal systems, nor have the metabolic products or primary eliminative routes in animal systems been examined. However, studies on mice at toxic dose levels provide evidence that benzotriazoles at sufficiently high doses severely affect the central nervous system.

Benzotriazole has been screened for tumor activity and has been found to be inhibiting against a strain of mammary adenocarcinoma and other tumors (Anon., 1958; Tarnowski and Bates, 1961). Negative results on inhibition of the same type of tumor have also been reported (Gellhorn et al., 1953). Any tumor inhibitory activity which benzotriazole may possess is probably related to its ability to disrupt purine metabolism, which results in impeding nucleic acid synthesis in tumor cells. Benzotriazoles have been shown to possess purine antagonist properties in bacterial studies (Greer, 1958).

Benzotriazoles may present a severe respiratory hazard if inhaled (Sherwin-Williams Co., 1976). Studies of rats indicate that severe local respiratory damage, rather than absorption and systemic poisoning, is responsible for the high toxicity of benzotriazole dusts. The dust is also a severe explosion hazard (Dorsett and Nagy, 1968). In situations outside the manufacturing or direct usage environments, it is not likely that exposure to benzotriazole dusts would occur.

Several benzotriazole derivatives not only exert profound inhibitory effects on bacterial growth, but are also mutagenic to certain bacterial species (Greer, 1958). The particular derivatives studied are not among the currently important commercial benzotriazoles. Although mutagenic chemicals are frequently carcinogenic (Miller and Miller, 1975), there is no direct evidence yet available to indicate whether benzotriazole or its derivatives may present a carcinogenic threat to man. Because of its potential effect on nucleic acid synthesis and metabolism, and its actions on the growth of bacterial and cancer cells, benzotriazole may be implicated as a tumorigen. Carcinogenesis testing of benzotriazole is presently under way at the National Cancer Institute (Weisburger, 1976), with results expected to be available in late 1976.

Benzotriazole has a cumulative toxic effect on certain tested young fresh water fish at concentration levels on the order of 12-25 ppm (Sherwin-Williams Co., 1975). It has been shown to inhibit embryo development in _Rana_ _pipiens_ (Liedke _et_ _al_., 1954, 1955). Benzotriazole also inhibits plant growth (Davis, 1954), bacterial growth (Foley, 1958), fungal growth (Loveless _et_ _al_., 1954), and viral growth (Tamm _et_ _al_., 1961). These growth inhibiting phenomena are generally attributed to the tested compound's purine antagonist properties. Levels of tolyltriazole, for example, above 20 ppm in wastewater would probably significantly increase the toxicity of the medium to lower vertebrate and invertebrate species, as well as increase oxygen demand (Sherwin-Williams Co., 1975).

No regulations currently exist for pesticide, food, or drug applications of benzotriazole. Several restrictions have been placed on the use of 2-(2'-hydroxyphenyl)-benzotriazoles as UV stabilizers for plastic food containers. The concentration of the stabilizer is limited to 0.25-0.50% (depending on the olefin or polystyrene substrate), and the foodstuff must be nonalcoholic and fat-free.

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CONCLUSIONS AND RECOMMENDATIONS

On the whole, it appears from the available evidence that benzotriazoles of current commercial significance present no particularly serious health or environmental hazards at present use levels and applications. However, this conclusion must be tempered with the understanding that a great deal is as yet unknown about the subacute effects of benzotriazoles in plant and animal systems, and especially in man. Market studies indicate the production of benzotriazoles is increasing and may be more than doubled by the end of this decade. Significantly increased usage of benzotriazoles could affect their status as environmental hazards, especially to aquatic life, for which benzotriazoles may be more of a hazard than for man. Currently, benzotriazoles enter the environment mainly via discarded antifreeze and discarded plastic products which have been UV-stabilized with benzotriazoles. A significant increase in certain other uses (for example as UV stabilizers in oil-based insecticides) could result in additional environmental loading.

Animal tests have shown that benzotriazole dust is a respiratory hazard. It is also an explosion hazard. In spite of this, no standards have been set for benzotriazoles for threshold or exposure limit values in (at least) the workroom environment by any of the agencies or groups responsible for such standards. Standards are also lacking for those few uses which place benzotriazoles directly into the environment. Of course, the setting of such standards would depend heavily on the status of benzotriazole and its derivatives as serious poisons or tumorigens, the possibility of which is indicated by their apparent ability to disrupt nucleic acid synthesis or endogenous purine utilization. Carcinogenicity testing of benzotriazoles is currently underway.

These studies are well warranted and their results ought to have a major impact on the regulatory standards for benzotriazoles which should be forthcoming thereafter.

In summary, industrial experience with benzotriazoles has been good. Nevertheless, the environmental consequences of current use patterns cannot presently be evaluated due to the lack of sufficient monitoring data. Since these compounds are likely to be persistent if placed in the environment, selective effluent and ambient monitoring of benzotriazoles would be desirable, along with the simultaneous development of information on the chemical and biological interaction of benzotriazoles with living systems.